(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 1 325 920 A1

(12) **EUROPEAN PATENT APPLICATION**
published in accordance with Art. 158(3) EPC

(43) Date of publication:
09.07.2003 Bulletin 2003/28

(21) Application number: **01967708.7**

(22) Date of filing: **17.09.2001**

(51) Int Cl.[7]: **C07D 333/62**, C07D 409/12, C07D 413/12, C07D 417/12, A61K 31/381, A61K 31/4025, A61K 31/4178, A61K 31/422, A61K 31/427, A61P 43/00, A61P 9/10

(86) International application number:
PCT/JP01/08061

(87) International publication number:
WO 02/022595 (21.03.2002 Gazette 2002/12)

(84) Designated Contracting States:
AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE TR
Designated Extension States:
AL LT LV MK RO SI

(30) Priority: **18.09.2000 JP 2000282046**
20.04.2001 JP 2001122972

(71) Applicant: **TOA EIYO LTD.**
Chuo-ku Tokyo 104-0031 (JP)

(72) Inventors:
- **SATOH, S., TOA Eiyo Ltd., Tokyo Resch Lab.**
  Saitama-shi, Saitama 330-0834 (JP)
- **TATSUI, Akira,**
  TOA Eiyo Ltd. Fukushima Res. Lab
  Fukushima-shi, Fukushima 960-0211 (JP)
- **HASEGAWA, T.,**
  TOA Eiyo Ltd. Fukushima Resch Lab.
  Fukushima-shi, Fukushima 960-0211 (JP)
- **YAMADA, H, TOA Eiyo Ltd. Tokyo Resch Lab.**
  Saitama-shi, Saitama 330-0834 (JP)
- **KAZAYAMA, Shin.,**
  TOA Eiyo Ltd. Tokyo Resch Lab.
  Saitama-shi, Saitama 330--0834 (JP)
- **MORITA, T., TOA Eiyo Ltd. Tokyo Resch Lab.**
  Saitama-shi, Saitama 330-0834 (JP)
- **MASAKI, H., TOA Eiyo Ltd. Tokyo Resch Lab.**
  Saitama-shi, Saitama 330-0834 (JP)
- **TAKAHASHI, A.,**
  TOA Eiyo Ltd. Tokyo Resch Lab.
  Saitama-shi, Saitama 330-0834 (JP)

(74) Representative: **Albrecht, Thomas, Dr.**
Kraus & Weisert,
Thomas-Wimmer-Ring 15
80539 München (DE)

(54) N-SUBSTITUTED BENZOTHIOPHENESULFONAMIDE DERIVATIVES

(57) The present invention relates to an N-substituted benzothiophenesulfonamide derivative or a salt thereof and applications thereof. Furthermore, it provides an agent for preventing or treating cardiac or circulatory disease caused by abnormal increase of production of angiotensin II or endothelin I based on chymase activity, wherein the agent has a selective inhibitory action on chymase.

EP 1 325 920 A1

Description

FIELD OF THE INVENTION

[0001] The present invention relates to medicaments, especially N-substituted benzothiophenesulfonamide derivatives or salts thereof which selectively inhibit chymase, and chymase inhibitors containing the same as the active ingredient. Since the compounds have a selective inhibitory action on chymase, they are useful as agents for preventing or treating hypertension, hypercardia, cardiac failure, cardiac infarction, arteriosclerosis, diabetic or non-diabetic renal diseases, diabetic retinopathy, restenosis after percutaneous transluminal coronary angioplasty (hereinafter, abbreviated as PTCA), intimal thickening after bypass grafting, ischemic re-perfusion disorder, chronic rheumatism, keloid, psoriasis, allergy, inflammation, asthma, atopic dermatitis, solid tumors caused by abnormal increase of production of angiotensin II (hereinafter, abbreviated as Ang II) or endothelin I (hereinafter, abbreviated as ET-1) based on chymase activity.

BACKGROUND OF THE INVENTION

[0002] Since Ang II and ET-1 have a cell growth- accelerating action in addition to a blood pressure- elevating action, they are considered as causative agents or risk factors for diseases such as hypertension, hypercardia, cardiac infarction, arteriosclerosis, diabetic or non-diabetic renal diseases and restenosis after PTCA. Moreover, it is known that Ang II is formed from angiotensin I (hereinafter, abbreviated as Ang I) by angiotensin converting enzyme (hereinafter, abbreviated as ACE), and a large number of ACE inhibitors have been developed as agents for preventing or treating the above diseases. On the other hand, it is known that ET-1 is a physiologically active peptide composed of 21 amino acid residues (hereinafter, abbreviated as ET(1-21)) which is formed from big endothelin (hereinafter, abbreviated as Big ET-1) by endothelin converting enzyme (hereinafter, abbreviated as ECE), but ECE inhibitors and ET-1 receptor antagonists are still in developmental stages as medicaments.

[0003] Recently, in addition to ACE, an enzyme producing Ang II from Ang I has been discovered and named chymase. Urata et al. purified chymase from human heart and has shown that 70 to 80% amount of Ang II produced in heart and blood vessels was due to chymase (J. Biol. Chem., 265, 22348 (1990). Moreover, when the fact that no effectiveness of ACE inhibitors on restenosis after PTCA is observed [MERCAPTOR study (Circulation, 86(1), 100 (1992)) and MARCAPTOR study (J. Am. Coll. Cardiol., 27(1), p. 1 (1996))] and the fact that chymase inhibitors are effective on a canine intimal thickening model of grafted blood vessel using jugular vein (Miyazaki, Takai et al.; Febs. Lett., 467, 141 (2000)) are together considered, it is important to inhibit chymase rather than ACE for preventing and treating cardiac and circulatory diseases caused by abnormal increase of the production of Ang II and thus the application of chymase inhibitors to cardiac and circulatory diseases is suggested.

[0004] Furthermore, in the recent past, it has been revealed that chymase specifically degrades Big ET-1 into a physiologically active peptide composed of 31 amino acid residues (hereinafter, abbreviated as ET(1-31)). It has been reported that the ET(1-31) acts on the receptor on which original ET(1-21) acts, to cause bronchoconstriction and vasoconstriction (Kido et al.; J. Immunol., 159, 1987 (1997)). In this connection, with regard to the concentration in human blood, both of ET(1-31) and ET(1-21) have about the same distribution and activity, and after cardiac infarction, ET(1-31) increases more largely than ET(1-21) does, which is maintained for two weeks after the incidence (Tamaki, Nishisu et al.; Jpn. J. Pharmacol., 82(suppl I), 26 (2000)), and the fact suggests importance of inhibition of chymase and application of chymase inhibitors to cardiac and circulatory diseases.

[0005] Accordingly, chymase is considered to participate in production and degradation of physiologically active peptides, remodeling of extracellular matrix, network with cytokine, immunity, and the like and contribute to restoration of metabolic turnover. Thus, a chymase inhibitor is expected to apply to cardiac and circulatory diseases.

[0006] Moreover, as a result of administration of Ang II into a sponge in a hamster subdermally sponge-implanted model, removal of the sponge after 7 days, and measurement of hemoglobin content, vascularization was observed (mainly capillary vessels). When ovalbumin (10 μg/site/day) as an antigen is administered to a sensitized animal via sponge, vascularization occurs as in the case of Compound 48/80. This vascularization was also inhibited by chymostatin (Muramatsu et al.; J. Biol. Chem., 275(8), 5545 (2000)). The above results indicate that activation of mast cells by antigen stimulation can also cause vascularization, and chymase may be involved in this process. Thus, new roles of chymase are suggested in a variety of inflammatory allergy diseases. From such a viewpoint, a chymase inhibitor is expected to exhibit effects on solid tumors, diabetic retinopathy, rheumatoid arthritis and atherosclerosis.

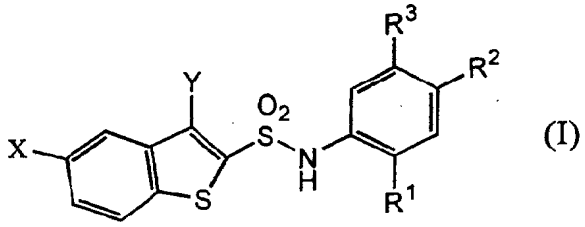
[0007] Currently, as inhibitors against chymase, peptide-type chymase inhibitors are disclosed in JP-A-10-7661, JP-A-11-49739, JP-A-11-246437, WO98/09949, WO98/18794, WO99/32459 and WO00/06594. On the other hand, non-peptide-type chymase inhibitors are disclosed in JP-A-10-87493, JP-A-10-245384, JP-A-12-95770, WO96/04248, WO97/11941, WO99/09977 WO00/03997, WO00/10982, WO00/32587. However, until now, no clinically applicable chymase inhibitor has been found. Accordingly, it is desired to develop a clinically applicable chymase inhibitor which

enables prevention and treatment of cardiac and circulatory diseases caused by abnormal increase of production of Ang II and ET-1.

DISCLOSURE OF THE INVENTION

[0008] As a result of the extensive studies for achieving the above objects, the present inventors have found that an N-substituted benzothiophenesulfonamide derivative or a pharmaceutically acceptable salt thereof has an excellent human chymase inhibitory activity and enzyme selectivity, and is stable even in rat blood plasma.

[0009] Namely, the invention relates to an N-substituted benzothiophenesulfonamide derivative represented by formula (I):

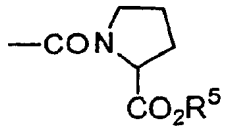


(I)

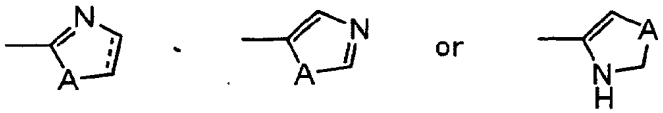
wherein X represents a hydrogen atom, a halogen atom or a lower alkyl group;

Y represents a lower alkyl group;

R^1 and R^2 each may be the same or different and represents a hydrogen atom, a lower alkoxycarbonyl group, a lower alkylsulfonyl group, a benzoyl group, an acyl group having 1 to 4 carbon atoms, a lower alkoxy group, a lower alkoxycarbonylmethylthioacetyl group, a nitro group, $-CONHR^4$ in which R^4 represents a hydrogen atom, a lower alkoxycarbonylmethyl group, a carboxymethyl group or $-CH(CH_2OH)COOR^5$ in which R^5 represents a hydrogen atom or a lower alkyl group, a group represented by formula:



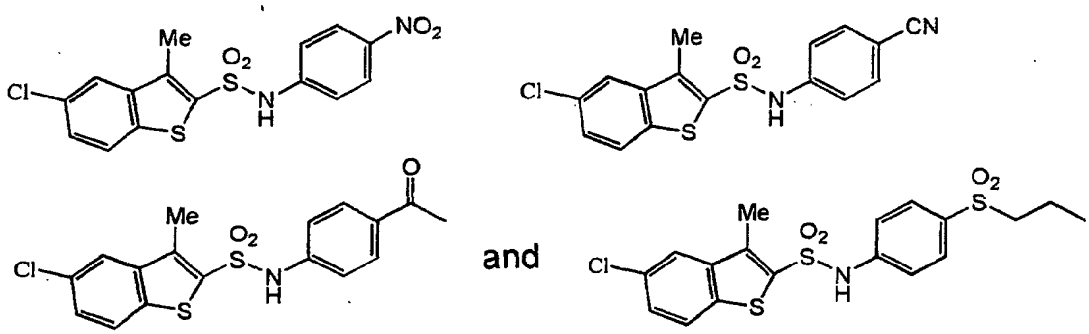
in which R^5 has the same meaning as above, a monocyclic heterocyclic group represented by formulae which may be substituted by $-CO_2R^5$ in which R^5 has the same meaning as above:



in which A represents an oxygen atom, a sulfur atom or NH and the dotted part represents a single bond or a double bond, a hydroxy lower alkyl group, a cyano group provided that R^1 and R^2 are not hydrogen atoms at the same time; and R^3 represents a hydrogen atom, a lower alkoxy group or a lower alkyl group, or a salt thereof.

[0010] The N-substituted benzothiophenesulfonamide derivative represented by formula (I) or a pharmaceutically acceptable salt thereof according to the invention has a strong inhibitory activity against chymase and is a extremely useful compound for preventing or treating cardiac or circulatory diseases caused by abnormal increase of production of Ang II or ET-1 based on chymase activity.

[0011] Also, it has been found that compounds represented by formulae



have a strong inhibitory activity against chymase and are extremely useful for preventing or treating cardiac or circulatory diseases caused by abnormal increase of production of Ang II or ET-1 based on chymase activity.

BEST MODE FOR CARRYING OUT THE INVENTION

[0012] Examples of the halogen atom for X include a fluorine atom, a chlorine atom, a bromine atom or an iodine atom, and particularly, a fluorine atom or a chlorine atom is preferable.

[0013] Examples of the lower alkyl group for X include a methyl group, an ethyl group, a propyl group, an isopropyl group, a butyl group, an isobutyl group, a sec-butyl group or a tert-butyl group, and particularly, a methyl group or an ethyl group is preferable.

[0014] Examples of the lower alkyl group for Y include a methyl group, an ethyl group, a propyl group, an isopropyl group, a butyl group, an isobutyl group, a sec-butyl group or a tert-butyl group, and particularly, a methyl group or an ethyl group is preferable.

[0015] Examples of the lower alkoxycarbonyl group for R^1 and R^2 include a methoxycarbonyl group, an ethoxycarbonyl group, a propoxycarbonyl group, an isopropoxycarbonyl group, a butoxycarbonyl group, an isobutoxycarbonyl group, a sec-butoxycarbonyl group or a tert-butoxycarbonyl group, and particularly, a methoxycarbonyl group, an ethoxycarbonyl group, an isopropoxycarbonyl group or a tert-butoxycarbonyl group is preferable.

[0016] Examples of the lower alkylsulfonyl group for R^1 and R^2 include a methanesulfonyl group, an ethanesulfonyl group, a propanesulfonyl group, an isopropanesulfonyl group, a butanesulfonyl group, an isobutanesulfonyl group, a sec-butanesulfonyl group or a tert-butanesulfonyl group, and particularly, a methanesulfonyl group or an ethanesulfonyl group is preferable.

[0017] Examples of the acyl group having 1 to 4 carbon atoms for R^1 and R^2 include a formyl group, an acetyl group, a propionyl group, a butyryl group or an isobutyryl group, and particularly, an acetyl group is preferable.

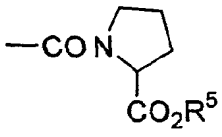
[0018] Examples of the lower alkoxy group for R^1, R^2 and R^3 include a methoxy group, an ethoxy group, a propoxy group, an isopropoxy group, a butoxy group, an isobutoxy group, a sec-butoxy group or a tert-butoxy group, and particularly, a methoxy group or an ethoxy group is preferable.

[0019] Examples of the lower alkoxycarbonylmethylthioacetyl group for R^1 and R^2 include a methoxycarbonylmethylthioacetyl group, an ethoxycarbonylmethylthioacetyl group, a propoxycarbonylmethylthioacetyl group, an isopropoxycarbonylmethylthioacetyl group, a butoxycarbonylmethylthioacetyl group, an isobutoxycarbonylmethylthioacetyl group, a sec-butoxycarbonylmethylthioacetyl group or a tert-butoxycarbonylmethylthioacetyl group, and particularly, a methoxycarbonylmethylthioacetyl group or an ethoxycarbonylmethylthioacetyl group is preferable.

[0020] In the case that R^1 and R^2 each is $-CONHR^4$, examples of the lower alkoxycarbonylmethyl group for R^4 include a methoxycarbonylmethyl group, an ethoxycarbonylmethyl group, a propoxycarbonylmethyl group, an isopropoxycarbonylmethyl group, a butoxycarbonylmethyl group, an isobutoxycarbonylmethyl group, a sec-butoxycarbonylmethyl group or a tert-butoxycarbonylmethyl group, and particularly, a methoxycarbonylmethyl group, an ethoxycarbonylmethyl group or an isopropoxycarbonylmethyl group is preferable.

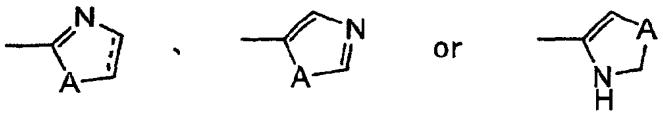
[0021] In the case that R^1 and R^2 each is $-CONHR^4$ and R^4 is $-CH(CR_2OH)COOR^5$, examples of the lower alkyl group for R^5 include a methyl group, an ethyl group, a propyl group, an isopropyl group, a butyl group, an isobutyl group, a sec-butyl group or a tert-butyl group, and particularly, a methyl group or an ethyl group is preferable.

[0022] In the case that R^1 and R^2 each is a group represented by formula:



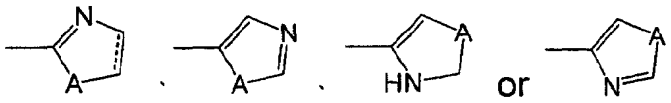
and R^5 is a lower alkyl group, examples of the lower alkyl group for R^5 is the same meaning as above.

[0023] In the case that R^1 and R^2 each is a monocyclic heterocyclic group represented by formulae which may be substituted by $-CO_2R^5$:

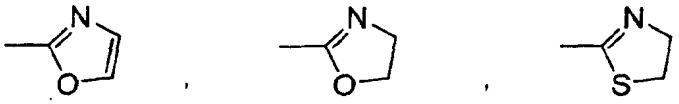


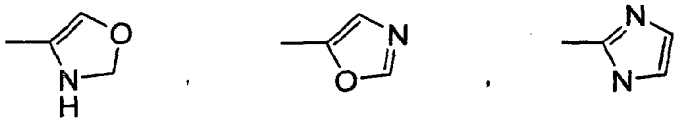
examples of the lower alkyl group for R^5 is the same meaning as above.

[0024] Examples of the monocyclic heterocylic group represented by the formulae which may be substituted:

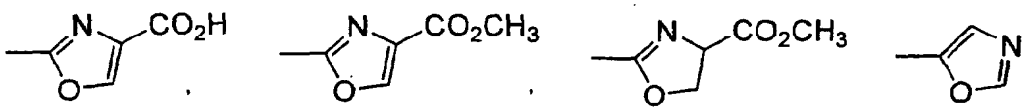


in which A represents an oxygen atom, a sulfur atom or NH and the dotted part represents a single bond or a double bond, include those represented by the following formulae.





[0025] Specific examples preferably include those represented by the formulae:



and these substituents are preferably substituted as R^2. In this case, it is further preferable that R^1 is a methanesulfonyl group and R^3 is a hydrogen atom.

[0026] Examples of the hydroxy lower alkyl group for R^1 and R^2 include a linear or branched hydroxy lower alkyl group having 1 to 4 carbon atoms such as a hydroxymethyl group, a hydroxyethyl group, a hydroxypropyl group or a hydroxybutyl group, and particularly, a hydroxymethyl group, a 1-hydroxyethyl group or a 2-hydroxyethyl group is preferable.

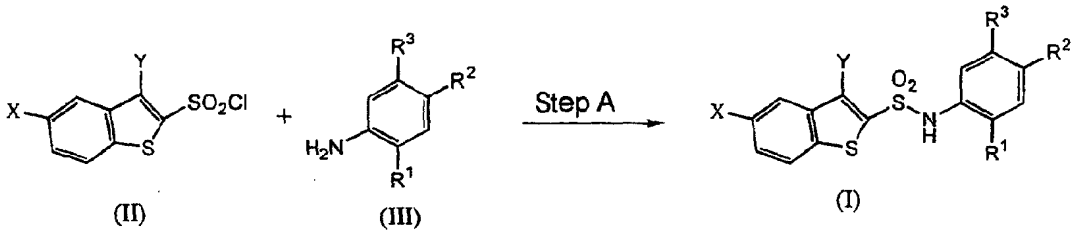
[0027] Examples of the lower alkyl group for R^3 include a methyl group, an ethyl group, a propyl group, an isopropyl

group, a butyl group, an isobutyl group, a sec-butyl group or a tert-butyl group, and particularly, a methyl group or an ethyl group is preferable.

[0028] In this regard, examples of specific compounds include methyl 4-(5-chloro-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methanesulfonylbenzoate, sodium methyl 4-(5-chloro-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methanesulfonylbenzoate, isopropyl 4-(5-chloro-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methanesulfonylbenzoate, 5-chloro-3-methylbenzo[b]thiophene-2-sulfonic acid (4-acetyl-2-methanesulfonylphenyl)amide, 5-chloro-3-methylbenzo[b]thiophene-2-sulfonic acid (4-benzoyl-2-methanesulfonylphenyl)amide, ethyl 4-(5-chloro-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methanesulfonylbenzoate, tert-butyl 4-(5-chloro-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methanesulfonylbenzoate, methyl 4-(5-chloro-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-ethanesulfonylbenzoate, methyl 4-(5-chloro-3-methylbenzo[b]thiophene-2-sulfonylamino)-5-methanesulfonyl-2-methylbenzoate, dimethyl 4-(5-chloro-3-methylbenzo[b]thiophene-2-sulfonylamino)isophthalate, methyl 4-(5-chloro-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methoxybenzoate, methyl 4-(5-chloro-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-nitrobenzoate, ethyl 4-(5-chloro-3-methylbenzo[b]thiophene-2-sulfonylamino) benzoate, 5-chloro-3-methylbenzo[b]thiophene-2-sulfonic acid (2,4-dimethanesulfonylphenyl)amide, 5-chloro-3-methylbenzo[b]thiophene-2-sulfonic acid (4-acetyl-2-nitrophenyl)amide, 5-chloro-3-methylbenzo[b]thiophene-2-sulfonic acid (4-hydroxymethyl-2-methanesulfonylphenyl)amide, 5-chloro-3-methylbenzo[b]thiophene-2-sulfonic acid (4-benzoylphenyl) amide, 5-chloro-3-methylbenzo[b]thiophene-2-sulfonic acid (2-methanesulfonylphenyl)amide, methyl 4-(5-fluoro-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methanesulfonylbenzoate, methyl 4-(5-methyl-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methanesulfonylbenzoate, 5-fluoro-3-methylbenzo[b]thiophene-2-sulfonic acid (4-acetyl-2-methanesulfonylphenyl) amide, methyl 4-(3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methanesulfonylbenzoate, methyl 2-[4-(5-chloro-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methanesulfonylphenyl]oxazole-4-carboxylate, methyl 2-[4-(5-fluoro-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methanesulfonylphenyl]oxazole-4-carboxylate, 2-[4-(5-chloro-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methanesulfonylphenyl]oxazole-4-carboxylic acid, 2-[4-(5-fluoro-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methanesulfonylphenyl]oxazole-4-carboxylic acid, disodium 2-[4-(5-chloro-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methanesulfonylphenyl]oxazole-4-carboxylate, disodium 2-[4-(5-fluoro-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methanesulfonylphenyl]oxazole-4-carboxylate.

[0029] Of the above-described compounds, methyl 4-(5-chloro-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methanesulfonylbenzoate, sodium methyl 4-(5-chloro-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methanesulfonylbenzoate, isopropyl 4- (5-chloro-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methanesulfonylbenzoate, 5-chloro-3-methylbenzo[b]thiophene-2-sulfonic acid (4-acetyl-2-methanesulfonylphenyl)amide, 5-chloro-3-methylbenzo[b]thiophene-2-sulfonic acid (4-benzoyl-2-methanesulfonylphenyl)amide, methyl 4-(5-fluoro-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methanesulfonylbenzoate, methyl 4-(5-methyl-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methanesulfonylbenzoate, 5-fluoro-3-methylbenzo[b]thiophene-2-sulfonic acid (4-acetyl-2-methanesulfonylphenyl)amide, methyl 4-(3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methanesulfonylbenzoate, 2-[4-(5-chloro-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methanesulfonylphenyl]oxazole-4-carboxylic acid, 2-[4-(5-fluoro-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methanesulfonylphenyl]oxazole-4-carboxylic acid, disodium 2-[4-(5-chloro-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methanesulfonylphenyl]oxazole-4-carboxylate, disodium 2-[4-(5-fluoro-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methanesulfonylphenyl]oxazole-4-carboxylate are preferable.

[0030] The following will describe the process for producing the N-substituted benzothiophenesulfonamide derivative or salt thereof of the invention. The compound of the general formula (I) of the invention can be produced through the production process as illustrated by the following reaction scheme.



(II) (III) (I)

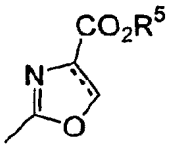
[0031] That is, in the scheme, the compound can be produced by reacting an amine represented by the formula (III) (in which R^1, R^2 and R^3 have the same meaning as defined in the formula (I)) with an sulfonyl chloride (II) in the presence of a base such as sodium amide, lithium amide, sodium hydride, potassium carbonate, potassium tert-butoxide, triethylamine, ethyldiisopropylamine, pyridine, or 1,8-diazabicyclo[5.4.0]undec-7-ene (hereinafter, abbreviated

as DBU) in a solvent such as dioxane, tetrahydrofuran (hereinafter, abbreviated as THF), acetone, dimethylformamide (hereinafter, abbreviated as DMF), dimethyl sulfoxide (hereinafter, abbreviated as DMSO), chloroform, pyridine or a mixed solvent thereof within the range of -10°C to a boiling point of the solvent.

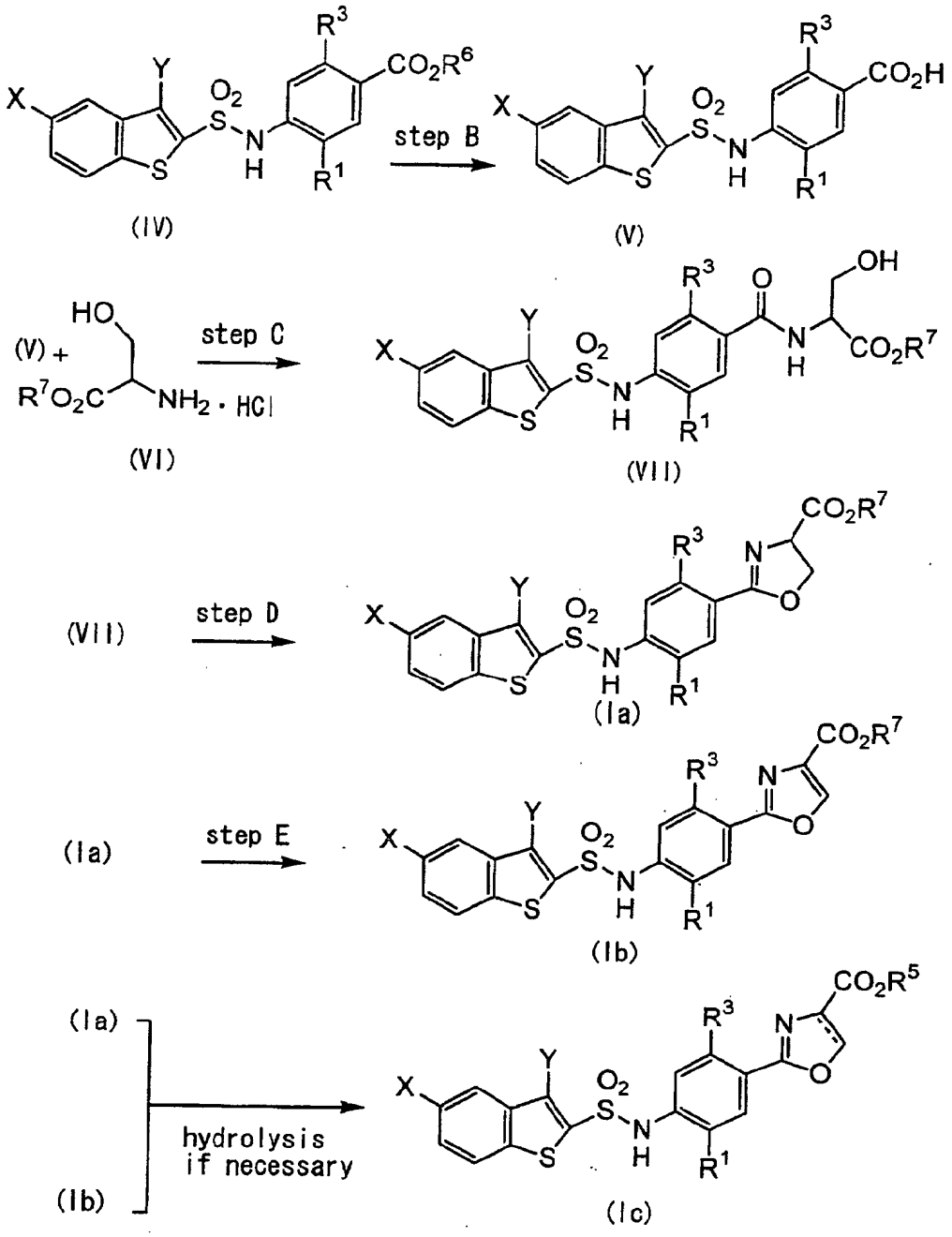
[0032] In this connection, in the case of the compound wherein R^1 and/or R^2 have an ester group, the compound of formula (I) can be further produced by reducing the ester group to form a hydroxymethyl group.

[0033] Moreover, in the case of the compound wherein R^1 and/or R^2 is -$CONHR^4$ and R^4 is a lower alkoxycarbonylmethyl group, the compound of formula (I) can be further produced after subjecting the compound to ester hydrolysis, and salt formation thereof can be also conducted.

[0034] Furthermore, for example, in the case of conducting the monocyclic heterocylic group as above, specifically the following group for R^2,



the following steps can be sequentially carried out.



[0035] A compound (V) wherein R^2 is CO_2H can be produced by subjecting a compound (IV) wherein R^2 is CO_2R^6 (R^6 represents a lower alkyl group) to ester hydrolysis (Step B). Thereafter, the compound (VII) is obtained by reacting the compound (V) with serine ester hydrochloride (VI) wherein R^7 represents a lower alkyl group, in the presence of a base such as triethylamine, ethyldiisopropylamine or DBU using a condensing agent such as N,N'-dicyclohexylcarbodiimide or 1-ethyl-3-(3-dimethylaminopropylcarbodiimide (hereinafter, abbreviated as EDC) (Step C), and then a

compound (Ia) and a compound (Ib) are obtained in accordance with the method known in literatures (Tetrahedron Letters, 33, 907 (1992), J. Org. Chem., 38, 26 (1973), J. Org. Chem., 58, 4494 (1993), Org. Lett., 2, 1165 (2000)) (Steps F and G), whereby the production is completed.

[0036] Furthermore, the compound (Ia) and the compound (Ib) are subjected to ester hydrolysis, if necessary. Thus, the compound represented by formula (Ic) can be produced. Moreover, salt formation thereof can be conducted.

[0037] The thus formed compound of formula (I) can be isolated and purified by conventional methods such as recrystallization and column chromatography.

[0038] The present invention includes a salt of the compound of formula (I). Examples of the salt of the compound of formula (I) are preferably pharmaceutically acceptable salts in view of use for a medicament.

[0039] Specific examples of the salt include a pharmaceutically acceptable salt with an acid or base, e.g., a salt with an inorganic acid such as hydrochloride, hydrobromide, hydroiodide, sulfate, nitrate or phosphate; a salt with an organic acid such as acetate, trifluoroacetate, oxalate, fumarate, maleate, tartrate, mesylate or tosylate; a salt with an alkali metal such as sodium salt or potassium salt; or a salt with an alkaline earth metal such as calcium salt depending on the compound, by a usual method.

[0040] The compound of formula (I) and a pharmaceutically acceptable salt thereof are useful as a agent for a chymase inhibitor.

[0041] The compound of formula (I) sometimes includes optical isomers based on an asymmetric carbon atom. These various types of isomers isolated and mixtures of these isomers are also encompassed within the invention. Moreover, the compound of formula (I) of the invention includes hydrates and various solvates. All the crystal forms are also encompassed within the compound of formula (I).

[0042] The invention also includes a medicament containing the N-substituted benzothiophenesulfonamide derivative represented by the above formula (I) or a pharmaceutically acceptable salt thereof. The medicament includes an agent for inhibiting chymase activity.

[0043] The medicament is effective for diagnosing, preventing and/or treating diseases caused by abnormal increase of production of angiotensin II or endothelin I.

[0044] The above-described diseases include circulatory diseases and inflammatory allergosis.

[0045] Specifically, the diseases include hypertension, hypercardia, cardiac failure, cardiac infarction, arteriosclerosis, diabetic or non-diabetic renal disease, diabetic retinopathy, ischemic re-perfusion disorder, restenosis after percutaneous transluminal coronary angioplasty, intimal thickening after bypass grafting, chronic rheumatism, keloid, psoriasis, allergy, inflammation, asthma, atopic dermatitis, or solid tumors.

[0046] The compound of formula (I) or a pharmaceutically acceptable salt thereof may be administered orally or parenterally (e.g. injection into a vein or intramuscular injection).

[0047] Examples of preparations for oral administration include tablets including sugar-coated tablets and film-coated tablets, pills, granules, powders, capsules including soft capsules, syrups, emulsions, suspensions, and the like.

[0048] The preparations for oral administration can be manufactured with mixing additives usually employed in the pharmaceutical field in accordance with a known method. Examples of such additives include an excipient such as lactose, mannitol or anhydrous calcium hydrogen phosphate; a binder such as hydroxypropyl cellulose, methyl cellulose or polyvinylpyrrolidone; a disintegrator such as starch and carboxymethyl cellulose; a lubricant such as magnesium stearate or talc; and the like.

[0049] Examples of preparations for parenteral administration include injections.
These injections can be manufactured by a common method, for example, by dissolving the compound of formula (I) or a pharmaceutically acceptable salt thereof in Japanese Pharmacopoeia-grade water for injection. As needed, an isotonic agent such as sodium chloride, a buffering agent such as sodium dihydrogen phosphate or sodium monohydrogen phosphate, or the like may be mixed.

[0050] The dose of the compound of formula (I) per day for an adult can be appropriately changed depending on the conditions, body weight, age of an individual patient, and a kind of a compound, route of administration the like, and the dose is suitably from about 1 mg to 1000 mg, preferably about 10 mg to 300 mg in the case of oral administration.

[0051] In the case of parenteral administration, the dose may be from one tenth to a half of the dose in the case of oral administration. The dose can be appropriately changed depending on the conditions, body weight, age and the like of an individual patient.

EXAMPLES

[0052] The following will describe the invention in more detail with Reference Examples and Examples, but the invention is not limited thereto.

Example 1

Methyl 4-(5-chloro-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methanesulfonylbenzoate

[0053] Into a mixed solvent of 20 mL of THF and 3 mL of DMF was dissolved 985 mg of methyl 4-amino-3-methanesulfonylbenzoate, followed by addition of 170 mg of sodium hydride (oily, 60%) at 0°C. After 20 minutes of stirring at the same temperature, 1.28 g of 5-chloro-2-chlorosulfonyl-3-methylbenzo[b]thiophene was added at 0°C, followed by 1 hour of stirring at room temperature. Further, 150 mg of sodium hydride (oily, 60%) was added at room temperature and the mixture was stirred for 2 hours at the same temperature. After confirmation of disappearance of the starting material, the reaction was terminated by adding saturated aqueous ammonium chloride solution at 0°C, followed by extraction with ethyl acetate. The organic layer was washed with saturated brine and then dried over anhydrous sodium sulfate. The solvent was removed by evaporation and the residue was purified by silica gel chromatography (ethyl acetate/hexane = 3/1) to obtain 911 mg of the title compound as colorless powder.
Melting point: 179-181°C
^{1}H-NMR ($CDCl_3$) : δ 2.70 (3H,s) ,3.06 (3H,s) ,3.90 (3H,s) ,7.48 (1 H,dd,J=2.1,8.6Hz) ,7.74 (1H,d,J=8.6Hz) ,7.89 (1H, d,J=2.1Hz) ,7. 86 (1H,d,J=8.8Hz) ,8.19 (1H,dd,J=2.0,8.8Hz) ,8.50 (1H,d,J=2.0Hz) ,9.84 (1H,s). IR ν_{max} (KBr) : 3217,1720,1608,1504,1442,1392,1308,1165,1119 c m^{-1}.

Example 2

Ethyl 4-(5-chloro-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methanesulfonylbenzoate

[0054] In the same manner as in Example 1, 529 mg of the title compound was obtained as colorless powder from 559 mg of ethyl 4-amino-3-methanesulfonylbenzoate.
Melting point: 167-169°C
^{1}H-NMR ($CDCl_3$) : δ 1.36 (3H,t,J=7.1Hz) ,2.70 (3H,s) ,3.06 (3H, s) ,4.36 (2H,q,J=7.1Hz) ,7.47 (1H,dd,J=2.0,8.8Hz) , 7.74 (1H,d,J= 8.8Hz) ,7.78 (1H,d,J=2.0Hz) ,7.86 (1H,d,J=8.8Hz) ,8.19 (1H,dd,J =2.0,8.8Hz) ,8.50 (1H,d,J=2.0Hz) , 9.83 (1H,brs). IR ν_{max} (KBr) :3224,2985,1716,1608,1500,1358,1300,1142 cm^{-1}.

Example 3

Tert-butyl 4-(5-chloro-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methanesulfonylbenzoate

[0055] In the same manner as in Example 1, 148 mg of the title compound was obtained as colorless powder from 128 mg of tert-butyl 4-amino-3-methanesulfonylbenzoate.
Melting point: 236-238°C
^{1}H-NMR ($CDCl_3$) : δ 1.54 (9H,s) ,2.52 (3H,s) ,3.28 (3H,s) ,7.55-7 .80 (4H,m) ,8.00 (1H,s) ,8.25-8.30 (1H,m). IR ν_{max} (KBr) :3467,2974,2327,1705,1662,1597,1477,1396,1296, 1130,1099cm^{-1}.

Example 4

Methyl 4-(5-chloro-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-ethanesulfonylbenzoate

[0056] In the same manner as in Example 1, 80 mg of the title compound was obtained as colorless powder from 76 mg of methyl 4-amino-3-ethanesulfonylbenzoate.
Melting point: 172-173°C
^{1}H-NMR ($CDCl_3$) : δ 1.27 (3H,t,J=7.3Hz) ,2.74 (3H,s) ,3.24 (2H,q, J=7.3Hz) ,3.77 (3H,s) ,7.20-7.31 (2H,m) ,7.43-7.56 (3H,m) ,8.31 (1H,s) .
IR ν_{max} (KBr) :3482,3217,2931,1709,1597,1481,1439,1284,1126 c m^{-1}.

Example 5

Methyl 4-(5-chloro-3-methylbenzo[b]thiophene-2-sulfonylamino)-5-methanesulfonyl-2-methylbenzoate

[0057] Into 10 mL of THF was dissolved 135 mg of methyl 4-amino-5-methanesulfonyl-2-methylbenzoate, followed by addition of 22 mg of sodium hydride (oily, 60%) at room temperature. After 20 minutes of stirring at the same temperature, 130 mg of 5-chloro-2-chlorosulfonyl-3-methylbenzo[b]thiophene was added at 0°C, followed by 1 hour of stirring at room temperature and 5 hours of heating under refluxing. Further, 1 mL of DMF, 22 mg of sodium hydride

(oily, 60%) and 50 mg of 5-chloro-2-chlorosulfonyl-3-methylbenzo[b]thiophene were added and the mixture was heated under refluxing for 2.5 hours. After confirmation of disappearance of the starting material, the reaction was terminated by adding saturated aqueous ammonium chloride solution at 0°C, followed by extraction with ethyl acetate. The organic layer was washed with saturated brine and then dried over anhydrous sodium sulfate. The solvent was removed by evaporation and the residue was purified by silica gel chromatography (ethyl acetate/hexane = 3/2) to obtain 102 mg of the title compound as colorless powder.

Melting point: 205-207°C

^{1}H-NMR ($CDCl_3$) : δ 2.65 (3H,s) ,2.71 (3H,s) ,3.04 (3H,s) ,3.87 (3 H,s) ,7.49 (1H,dd,J=2.0,8.6Hz) ,7.68 (1H,s) ,7.77 (1H,d,J=8.6Hz) ,7.80 (1H,d, J=2.0Hz) ,8.42 (1H,s) ,9.73 (1H,s).

IR ν_{max} (KBr) :3259,1728,1604,1554,1504,1439,1385,1354,1300,1 257,1157,1092 cm^{-1}.

Example 6

Dimethyl 4-(5-chloro-3-methylbenzo[b]thiophene-2-sulfonylamino isophthalate

[0058] Into 8 mL of THF was dissolved 115 mg of dimethyl 4-aminoisophthalate, followed by addition of 22 mg of sodium hydride (oily, 60%). After 20 minutes of stirring at room temperature, 130 mg of 5-chloro-2-chlorosulfonyl-3-methylbenzo[b]thiophene was added at the same temperature, followed by 30 minutes of stirring at room temperature. Further, 26 mg of sodium hydride (oily, 60%) was added and the whole was heated under refluxing for 6 hours. After confirmation of disappearance of the starting material, the reaction was terminated by adding saturated aqueous ammonium chloride solution at 0°C, followed by extraction with ethyl acetate. The organic layer was washed with saturated brine and then dried over anhydrous sodium sulfate. The solvent was removed by evaporation and the residue was purified by silica gel chromatography (ethyl acetate/hexane = 1/1) to obtain 62 mg of the title compound as light yellow amorphous.

^{1}H-NMR ($CDCl_3$) : δ 2.64 (3H,s) ,3.88 (3H,s) ,3.95 (3H,s) ,7.44 (1 H,dd,J=2.0,8.8Hz) ,7.71 (1H,d,J=8.8Hz) ,7.74 (1H, d,J=2.0Hz) ,7. 86 (1H,d,J=8.8Hz) ,8.11 (1H,dd,J=2.0,8.8Hz) ,8.63 (1H,d,J=2.0Hz) .

IR ν_{max} (KBr) : 3440,3140,2954,1724,1693,1608,1500,1439,1331,1 246,1165,1119 cm^{-1}.

Example 7

Methyl 4-(5-chloro-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methoxybenzoate

[0059] Into 4 mL of pyridine were dissolved 120 mg of methyl 4-amino-3-methoxybenzoate and 150 mg of 5-chloro-2-chlorosulfonyl-3-methylbenzo[b]thiophene, followed by 14 hours of stirring at room temperature. After confirmation of disappearance of the starting material, the reaction was terminated by adding water at 0°C, followed by extraction with ethyl acetate. The organic layer was washed with saturated brine and then dried over anhydrous sodium sulfate. The solvent was removed by evaporation and then the residue was purified by silica gel chromatography (chloroform/methanol = 9/1) to obtain 110 mg of the title compound as colorless amorphous.

^{1}H-NMR ($CDCl_3$) : δ 2.55 (3H,s) ,3.79 (3H,s) ,3.86 (3H,s) ,7.42 (1 H,dd,J=2.0,8.6Hz) ,7.45 (1H,dd,J=2.0,8.6 Hz) ,7.61 (1H,d,J=2.0H z) ,7.62 (1H,d,J=8.6Hz) ,7.68 (1H,d,J=8.6Hz) ,7.71 (1H,d,J=2.0H z)

IR ν_{max} (KBr) : 3248,2951,1716,1601,1512,1439,1350,1284,1242,1 161,1115 cm^{-1}.

Example 8

Methyl 4-(5-chloro-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-nitrobenzoate

[0060] In the same manner as in Example 6, 146 mg of the title compound was obtained as yellow powder from 122 mg of methyl 4-amino-3-nitrobenzoate.

Melting point: 164-165°C

^{1}H-NMR ($CDCl_3$) : δ 2,47 (3H,s) ,3.84 (3H,s) ,7.56 (1H,d,J=8.6Hz) ,7.57 (1H,brd,J=8.6Hz) ,8.01 (1H,d,J=1.8Hz) ,8.06 (1H,d,J=8.6 Hz) ,8.07 (1H,brd,J=8.6Hz) ,8.25 (1H,d,J=1.8Hz). IR ν_{max} (KBr) : 3442,3237,3060,2949,1732,1621, 1535,1507,1440,1 356,1297,1164,1106 cm^{-1}.

Example 9

5-chloro-3-methylbenzo[b]thiophene-2-sulfonic acid (2,4-dimethanesulfonylphenyl)amide

[0061] In the same manner as in Example 6, 368 mg of the title compound was obtained as colorless powder from

200 mg of 2,4-dimethanesulfonylaniline.
Melting point: 176-178°C
^{1}H-NMR (DMSO-d_6) : δ 2,65 (3H,s) ,3.00 (3H,s) ,3.07 (3H,s) ,7.44 (1H,dd,J=1.8,8.6Hz) ,7.71 (1H,d,J=8.6Hz) ,7.76 (1H,d,J=1.8Hz) ,7.92 (1H,d,J=8.8Hz) ,8.04 (1H,dd,J=1.8,8.8Hz) ,8.34 (1H,d,J=1. 8Hz) .
IR ν_{max} (KBr) : 3236,3020,1593,1489,1392,1354,1304,1157 cm^{-1}.

Example 10

5-chloro-3-methylbenzo[b]thiophene-2-sulfonic acid (4-acetyl-2-nitrophenyl)amide

[0062] In the same manner as in Example 6, 59 mg of the title compound was obtained as colorless powder from 96 mg of 4-acetyl-2-nitroaniline.
Melting point: 130-131°C
^{1}H-NMR ($CDCl_3$) : δ 2.58 (3H,s) ,2.69 (3H,s) ,7.46 (1H,dd,J=2.0,8 .6Hz) ,7.73 (1H,d,J=8.6Hz) ,7.78 (1H,d,J=2.0Hz) , 8.05 (1H,d,J=8 .8Hz) ,8.16 (1H,dd,J=1.8,8.8 Hz) ,8.74 (1H,d,J=1.8Hz).
IR ν_{max} (KBr) : 3795, 3479, 3363, 3262, 3089, 2927, 2858, 1689, 1620, 1 531,1419,1354,1115,1080 cm^{-1}.

Example 11

5-chloro-3-methylbenzo[b]thiophene-2-sulfonic acid (4-acetyl-2-methanesulfonylphenyl)amide

[0063] Into a mixed solvent of 20 mL of THF and 5 mL of DMF was dissolved 241 mg of 4-amino-3-methanesulfonylacetophenone, followed by addition of 136 mg of sodium hydride (oily, 60%) at -78°C. After 20 minutes of stirring at the same temperature, 350 mg of 5-chloro-2-chlorosulfonyl-3-methylbenzo[b]thiophene was added at -78°C, and the mixture was gradually warmed and stirred at -10°C for 1 hour. After confirmation of disappearance of the starting material, the reaction was terminated by adding saturated aqueous ammonium chloride solution at 0°C, followed by extraction with ethyl acetate. The organic layer was washed with saturated brine and then dried over anhydrous sodium sulfate. The solvent was removed by evaporation and the residue was purified by silica gel chromatography (ethyl acetate/hexane = 1/1) to obtain 427 mg of the title compound as colorless powder.
Melting point: 207-209°C
^{1}H-NMR ($CDCl_3$) : δ 2.56 (3H,s) ,2.69 (3H,s) ,3.07 (3H,s) ,7.46 (1H,dd,J=1.9,8.7Hz) ,7.72-7.79 (2H,m) ,7.86 (1H,d, J=8.6Hz) ,8.10 (1H,d,J=8.6Hz) ,8.40 (1H,d,J=1.9Hz).
IR ν_{max} (KBr) :3456,3236,3086,3005,2924,2854,1670,1593,1489,1 389,1354,1308,1261,1165,1130,1053 cm^{-1}.

Example 12

5-chloro-3-methylbenzo[b]thiophene-2-sulfonic acid (4-benzoyl-2-methanesulfonylphenyl)amide

[0064] In the same manner as in Example 11, 68 mg of the title compound was obtained as colorless powder from 94 mg of 4-amino-3-methanesulfonylbenzophenone.
Melting point: 144-146°C
^{1}H-NMR ($CDCl_3$) : δ 2.70 (3H,s) ,3.08 (3H,s) ,7.45-7.50 (3H,m) ,7 .58-7.62 (2H,m) ,7.68-7.71 (4H,m) ,7.85 (1H,d, J=8.6Hz) ,7.97 (1H ,d,J=8.6Hz) ,8.31 (1H,brs).
IR ν_{max} (KBr) :3456,3248,3001,2927,2858,2256,1709,1655,1597,1 496,1450,1389,1350,1308,1161,1130,1084 cm^{-1}.

Example 13

5-chloro-3-methylbenzo[b]thiophene-2-sulfonic acid (4-hydroxymethyl-2-methanesulfonylphenyl)amide

[0065] Into 10 mL of toluene was dissolved 305 mg of the compound of Example 1, and the solution was cooled to -78°C, followed by addition of 2.2 mL of 1.01 M toluene solution of diisobutylaluminum hydride. After 20 minutes of stirring at the same temperature, the mixture was gradually warmed to 0°C and stirred for 1 hour. After the reaction was terminated by adding water, the mixture was diluted with ethyl acetate and saturated aqueous potassium sodium tartrate solution were added, followed by 30 minutes of stirring at room temperature. The mixture was extracted with ethyl acetate and the organic layer was washed with saturated brine and then dried over anhydrous sodium sulfate. The solvent was removed by evaporation and the residue was purified by silica gel chromatography (ethyl acetate/hexane = 1/1) to obtain 230 mg of the title compound as colorless powder.
Melting point: 183-184°C

^{1}H-NMR ($CDCl_3$) : δ 1.83 (1H,brs) ,2.69 (3H,s) ,2.97 (3H,s) ,4.69 (2H,d,J=5.7Hz) ,7.47 (1H,dd,J=2.1Hz,8.7Hz) ,7.57 (1H,dd,J=2.1H z,8.7Hz) ,7.74 (1H,d,J=9.3Hz) ,7.78 (1H,d,J=9.3Hz) ,7.79 (1H,d, J=2.1Hz) ,7.86 (1H,d,J=2.1Hz) ,9.49 (1H,brs).
IR ν_{max} (KBr) :3563,3236,1612,1500,1392,1277,1142cm^{-1}.

Example 14

Ethyl 4-(5-chloro-3-methylbenzo[b]thiophene-2-sulfonylamino)benzoate

[0066] Into 3 mL of pyridine was dissolved 60 mg of ethyl 4-aminobenzoate, and 123 mg of 5-chloro-2-chlorosulfonyl-3-methylbenzo[b]thiophene was added at 0°C, followed by 2 hours of stirring at room temperature. After confirmation of disappearance of the starting material, 2 mol/L hydrochloric acid was added, followed by extraction with ether. The organic layer was washed with saturated brine and then dried over anhydrous magnesium sulfate. The solvent was removed by evaporation under reduced pressure and the resulting crude product was purified by silica gel column chromatography (ethyl acetate/hexane = 1/3) to obtain 80 mg of the title compound as light pink powder.
Melting point: 224-226°C
^{1}H-NMR (DMSO-d_6) : δ 1.26 (3H,t,J=7.1Hz) ,2.50 (3H,s) ,4.23 (2H, q,J=7.1Hz) ,7.27 (2H,d,J=8.8Hz) ,7.57 (1H,dd, J=2.0,8.6Hz) ,7.84 (2H,d,J=8.8Hz) ,8.01 (1H,d,J=2.0Hz) ,8.05 (1H,d,J=8.6Hz).
IR ν_{max} (KBr) : 3213,1696,1608,1511,1347,1288,1159 cm^{-1}.

Example 15

5-chloro-3-methylbenzo[b]thiophene-2-sulfonic acid (4-benzoylphenyl)amide

[0067] In the same manner as in Example 14, 187 mg of the title compound was obtained as colorless powder from 126 mg of 4-benzoylaniline.
Melting point: 198-200°C
^{1}H-NMR ($CDCl_3$) : δ 2.56 (3H,s) ,7.22-7.26 (2H,m) ,7.44-7.48 (3H, m) ,7.55-7.60 (1H,m) ,7.70-7.76 (6H,m).
IR ν_{max} (KBr) : 3213,2927,1724,1639,1589,1508,1450,1408,1288,1 234,1149 cm^{-1}.

Example 16

5-chloro-3-methylbenzo[b]thiophene-2-sulfonic acid (2-methanesulfonylphenyl)amide

[0068] In the same manner as in Example 14, 52 mg of the title compound was obtained as colorless powder from 100 mg of 2-methanesulfonylaniline.
Melting point: 191-193°C
^{1}H-NMR ($CDCl_3$) : δ 2.68 (3H,s) ,3.00 (3H,s) ,7.24-7.29 (1H,m) ,7 .35 (1H,s) ,7.74-7.80 (2H,m) ,7.46 (1H,dd, J=1.8,8.6Hz) ,7.74-7. 80 (1H,m) ,7.85 (1H,dd,J=1.5,7.9Hz) .
IR ν_{max} (KBr) :3467,3371,3228,3016,2927,2858,1712,1624,1566,1 485,1408,1288,1134,1026 cm^{-1}.

Example 17

Methyl 4-(5-fluoro-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methanesulfonylbenzoate

[0069] Into 300 mL of THF was dissolved 14.0g of methyl 4-amino-3-methanesulfonylbenzoate, followed by addition of 6.10 g of sodium hydride (oily, 60%) at 0°C. After 40 minutes of stirring at the same temperature, 16.0 g of 5-fluoro-2-chlorosulfonyl-3-methylbenzo[b]thiophene was added at 0°C, followed by 3 hours of stirring at room temperature. After confirmation of disappearance of the starting material, the reaction was terminated by adding 2 mol/L hydrochloric acid at 0°C, followed by extraction with ethyl acetate. The organic layer was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine and then dried over anhydrous sodium sulfate. The solvent was removed by evaporation and the residue was diluted with ethyl acetate. After the solution was treated with active carbon, purification by recrystallization (ethyl acetate/ether) afforded 24.8 g of the title compound as colorless powder.
Melting point: 202-204°C
^{1}H-NMR ($CDCl_3$) : δ 2.69 (3H,s) ,3.06 (3H,s) ,3.90 (3H,s) ,7.28 (1 H,ddd,J=2.6,8.7,8.9Hz) ,7.46 (1H,dd,J=2.6,9.2Hz) , 7.76 (1H,dd,J =4.7,8.9Hz) ,7.87 (1H,d,J=8.8Hz) ,8.19 (1H,dd,J=2.0,8.8Hz) ,8.5 0 (1H,d,J=2.0Hz) ,9.83 (1H,s).
IR ν_{max} (KBr) :3182,1724,1604,1504,1442,1396,1346,1303,1157 cm^{-1}.

Example 18

Methyl 4-(5-methyl-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methanesulfonylbenzoate

[0070] Into 8.0 mL of THF was dissolved 183 mg of methyl 4-amino-3-methanesulfonylbenzoate, followed by addition of 96 mg of sodium hydride (oily, 60%) at 0°C. After 20 minutes of stirring at the same temperature, 250 mg of 5-methyl-2-chlorosulfonyl-3-methylbenzo[b]thiophene was added at 0°C, followed by 6 hours of stirring at room temperature. After confirmation of disappearance of the starting material, the reaction was terminated by adding 1 mol/L hydrochloric acid at 0°C, followed by extraction with chloroform. The organic layer was washed with saturated brine and then dried over anhydrous sodium sulfate. The solvent was removed by evaporation and then the residue was purified by silica gel column chromatography (ethyl acetate/n-hexane = 3/1 to 1/1) to obtain 181 mg of the title compound as colorless powder. Melting point: 179-181°C

^{1}H-NMR ($CDCl_3$) : δ 2.48 (3H,s) ,2.70 (3H,s) ,3.02 (3H,s) ,3.89 (3 H,s) ,7.35 (1H,dd,J=2.2,8.8Hz) ,7.60 (1H,d, J=2.2Hz) ,7.69 (1H,d ,J=8.8Hz) ,7.88 (1H,d,J=8.8Hz) ,8.18 (1H,dd,J=1.8,8.8Hz) ,8.50 (1H,d,J=1.8Hz).

IR ν_{max} (KBr) :3460, 3178,3016,2927,2861,1724,1604,1500,1439, 1396,1300,1130,1061 cm^{-1}.

Example 19

5-fluoro-3-methylbenzo[b]thiophene-2-sulfonic acid (4-acetyl-2-methanesulfonylphenyl)amide

[0071] Into a mixed solvent of 168 mL of THF and 42 mL of DMF was dissolved 6.30 g of (4-amino-3-methanesulfonyl) acetophenone, followed by addition of 4.70 g of sodium hydride (oily, 60%) at -40°C. After 10 minutes of stirring at the same temperature, 8.60 g of 5-fluoro-2-chlorosulfonyl-3-methylbenzo[b]thiophene was added at the same temperature, followed by 4 hours of stirring at the same temperature. After confirmation of disappearance of the starting material, the reaction was terminated by adding 1 mol/L hydrochloric acid at the same temperature and then the mixture was rendered pH 1 with concentrated hydrochloric acid, followed by extraction with chloroform. The organic layer was washed with saturated brine and then dried over anhydrous sodium sulfate. The solvent was removed by evaporation and then the residue was diluted with chloroform. After the solution was treated with active carbon, the solvent was removed by evaporation and the resulting crystals were washed with methanol to obtain 10.9 g of the title compound as colorless powder.

Melting point: 174-175°C

^{1}H-NMR ($CDCl_3$) : δ 2.56 (3H,s) ,2.69 (3H,s) ,3.08 (3H,s) ,7.29 (1 H,ddd,J=2.5,8.8,8.8Hz) ,7.47 (1H,dd,J=2.5,8.8Hz) , 7.77 (1H,dd,J =4.6,8.8Hz) ,7.84 (1H,d,J=8.6Hz) ,8.12 (1H,dd,J=2.2,8.6Hz) ,8.4 2 (1H,d,J=2.2Hz) ,9.83 (1H,brs) .

IR ν_{max} (KBr) :3243,3092,3006,2925,1672,1599,1443,1392,1262, 1130,1056,1029 cm^{-1}.

Example 20

Methyl 4-(3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methanesulfonylbenzoate

[0072] Into a mixed solvent of 30 mL of methanol and 30 mL of dioxane was dissolved 640 mg of 5% palladium/carbon, followed by 10 minutes of stirring under a hydrogen atmosphere. Under an argon atmosphere, 330 mg of methyl 4-(5-chloro-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methanesulfonylbenzoate was added, followed by 3 days of stirring under a hydrogen atmosphere at 5 atm. After confirmation of disappearance of the starting material, the reaction mixture was filtered and purification by silica gel column chromatography (ethyl acetate/n-hexane = 2/1) to obtain 70 mg of the title compound as colorless powder.

Melting point: 170-172°C

^{1}H-NMR ($CDCl_3$) : δ 2.75 (3H,s) ,3.04 (3H,s) ,3.90 (3H,s) ,7.49 (1 H,dd,J=7.1,7.7Hz) ,7.51 (1H,dd,J=7.1,7.7Hz) ,7.83 (2H,d,J=7.7Hz) ,7.89 (1H,d,J=8.8Hz) ,8.20 (1H,dd,J=2.0, 8.8Hz) ,8.51 (1H,d,J =2.0Hz) ,9.82 (1H,s).

IR ν_{max} (KBr) :3209,1720,1604,1500,1442,1392,1350,1308,1165, 1122 cm^{-1}.

Example 21

Methyl (2S)-2-[4-(5-fluoro-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methanesulfonyl]benzoylamino-3-hydroxy-propionate

[0073] Into 450 mL of chloroform was dissolved 14.3 g of [4-(5-fluoro-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methanesulfonyl]benzoic acid obtained by hydrolysis of 24.8 g of methyl 4-(5-fluoro-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methanesulfonylbenzoate. After 7.54 g of L-serine methyl ester hydrochloride and 9.30 g of EDC

hydrochloride were added thereto at room temperature, 6.80 mL of triethylamine was added at 0°C. After 2 hours of stirring at the same temperature, the reaction was terminated by adding 2 mol/L hydrochloric acid at 0°C and the mixture was extracted with chloroform. The organic layer was washed with saturated brine and then dried over anhydrous sodium sulfate. The solvent was removed by evaporation and the residue was purified by silica gel chromatography (ethyl acetate) to obtain 12.9 g of the title compound as colorless amorphous.

^{1}H-NMR ($CDCl_3$) : δ 2.71 (3H,s) ,3.07 (3H,s) ,3.81 (3H,s) ,4.00 (1 H,dd,J=4.2,11.4Hz) ,4.15 (1R,dd,J=5.4,11.4Hz) ,4.85 (1H,dd,J=4. 2,5.4Hz) ,7.33 (1H,dd,J=2.1,8.6Hz) ,7.48 (1H,dd,J=2.1,8.6Hz) ,7 .79 (1H,dd,J=4.6,8.6Hz) ,7.87 (1H,d, J=8.8Hz) ,8.00 (1H,dd,J=2.1 ,8.8Hz) ,8.32 (1H,d,J=2.1Hz) ,9.76 (1H,s).

IR ν_{max} (KBr) :3401,1735,1655,1606,1510,1491,1440,1353,1308,1 164,1136cm^{-1}.

Example 22

Methyl 2-[4-(5-fluoro-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methanesulfonylphenyl]-4,5-dihydro-oxazole-4-carboxylate

[0074] Into 180 mL of THF was dissolved 12.9 g of methyl (2S)-2-[4-(5-fluoro-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methanesulfonyl]benzoylamino-3-hydroxy-propionate, and 6.80 g of Burgess reagent (J. Org. Chem., 38, 26, (1973); J. Org. Chem., 58, 4494 (1993)) was added, followed by 2 hours of stirring at 60°C. After confirmation of disappearance of the starting material, the solvent was removed by evaporation and water was added, followed by extraction with ethyl acetate. The organic layer was washed with saturated brine and then dried over anhydrous sodium sulfate. The solvent was removed by evaporation and the residue was purified by silica gel chromatography (ethyl acetate/hexane = 9/1) to obtain 9.92 g of the title compound as colorless amorphous.

^{1}H-NMR ($CDCl_3$) : δ 2.68 (3H,s) ,3.02 (3H,s) ,3.81 (3H,s), 4.60 (1H,dd,J=9.0,10.6Hz) ,4.69 (1H,dd,J=7.9,9.0Hz) ,4.93 (1H,dd,J=7. 9,10.6Hz) ,7.29 (1H,ddd,J=2.1,8.8,8.8Hz) ,7.46 (1H,dd,J=2.1,8.8 Hz) ,7.76 (1H,dd,J=4.6,8.8Hz) ,7.87 (1H,d,J=8.8Hz) ,8.15 (1H,dd ,J=2.1,8.8Hz) ,8.43 (1H,d,J=2.1Hz) ,9.81 (1H,s).

IR ν_{max} (KBr) :3226,1737,1647,1608,1498,1441,1395,1355,1308,1 248,1211,1164 cm^{-1}.

Example 23

Methyl 2-[4-(5-fluoro-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methanesulfonylphenyl]oxazole-4-carboxylate

[0075] Into 40 mL of dichloromethane was dissolved 1.10 g of methyl 2-[4-(5-fluoro-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methanesulfonylphenyl]-4,5-dihydro-oxazole-4-carboxylate, followed by addition of 498 mg of bromotrichloromethane at -20°C. Further, 700 mg of DBU was added dropwise at the same temperature and the whole was stirred at the same temperature for 5 minutes and then warmed to 0°C, followed by 3.5 hours of stirring. After confirmation of disappearance of the starting material, the reaction was terminated by adding saturated aqueous sodium hydrogen carbonate solution at 0°C, followed by extraction with ethyl acetate. The organic layer was washed with saturated brine and then dried over anhydrous magnesium sulfate. The solvent was removed by evaporation and the residue was purified by silica gel chromatography (ethyl acetate/methanol = 20/1) to obtain 597 mg of the title compound as colorless powder.

Melting point: 290-292°C

^{1}H-NNR ($CDCl_3$) : δ 2.70 (3H,s) ,3.06 (3H,s) ,3.95 (3H,s) ,7.30 (1 H,ddd,J=2.4,8.7,8.7Hz) ,7.47 (1H,dd,J=2.4,9.0Hz) , 7.77 (1H,dd,J =4.8,9.0Hz) ,7.94 (1H,d,J=9.0Hz) , 8.27 (1H,s) ,8.28 (1H,dd,J=2 .1,9.0Hz) ,8.57 (1H,d,J=2.1Hz) ,9.78 (1H,s).

IR ν_{max} (KBr) :3243,1720,1618,1590,1518,1485,1440,1355,1320,1 303,1259,1162,1136 cm^{-1}.

Example 24

2-[4-(5-fluoro-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methanesulfonylphenyl]oxazole-4-carboxylic acid

[0076] Into 150 mL of methanol was dissolved 7.85 g of methyl 2-[4-(5-fluoro-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methanesulfonylphenyl]oxazole-4-carboxylate, and 15 mL of 10% aqueous sodium hydroxide solution and 15 mL of water were added thereto at room temperature, followed by 15 minutes of stirring. The precipitated crystals were dissolved by adding 90 mL of water, and the solution was stirred at the same temperature for 17 hours. After the solvent was removed by evaporation, 45 mL of 1 mol/L hydrochloric acid was added to the residue, the precipitated crystals were collected by filtration and washed with water, and 100 mL of DMF was added to the resulting crude crystals, followed by heating under refluxing. After filtration at a hot state, 70 mL of ethanol was added and recrystallization was carried out. The resulting crystals were collected by filtration, washed several times with ethanol

and water alternatively, and dried over diphosphorus pentoxide under reduced pressure to obtain 5.78 g of the title compound as colorless powder.
Melting point: 289-291°C
^{1}H-NMR (DMSO-d_6) : δ 2.55 (3H,s) ,3.41 (3H,s) ,7.44 (1H,ddd,J=1. 8,8.7,9.0Hz) ,7.64 (1H,d,J=8.4Hz) ,7.79 (1H,dd, J=1.8,9.9Hz) ,8. 08 (1H,dd,J=4.8,8.7Hz) ,8.19 (1H,dd,J=1.8,8.4Hz) ,8.41 (1H,d,J= 1.8Hz) ,8.84 (1H,s).
IR ν_{max} (KBr) : 3232,1717,1690,1616,1487,1440,1355,1313,1161,1 140 cm^{-1}.

Example 25

Methyl 2-[4-(5-chloro-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methanesulfonylphenyl]oxazole-4-carboxylate

[0077] Into 10 mL of dichloromethane was dissolved 495 mg of copper dibromide, followed by addition of 310 mg of hexamethyltetramine at room temperature. Further, 337 mg of DBU was added dropwise at 0°C, the whole was stirred at the same temperature for 5 minutes and then methyl 2-[4-(5-chloro-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methanesulfonylphenyl]-4,5-dihydro-oxazole-4-carboxylate was added at 0°C, followed by 3 hours of stirring at room temperature. After confirmation of disappearance of the starting material, ethyl acetate was added to the reaction mixture. The organic layer was washed with a 1:1 mixed solution of saturated aqueous ammonium chloride solution and 25% aqueous ammonia solution, saturated aqueous sodium hydrogen carbonate and saturated brine and then dried over anhydrous magnesium sulfate. The solvent was removed by evaporation and the residue was purified by silica gel chromatography (chloroform/methanol = 10/1) to obtain 110 mg of the title compound as colorless powder.
Melting point: 237-239°C
^{1}H-NMR ($CDCl_3$) : δ 2.70 (3H,s) ,3.05 (3H,s) ,3.95 (3H,s) ,7.47 (1 H,dd,J=2.1,8.7Hz) ,7.74 (1H,d,J=8.7 Hz) ,7.79 (1H, d,J=2.1Hz) ,7 .93 (1H,d,J=9.0Hz) ,8.27 (1H,s) ,8.28 (1H,dd,J=2.1,9.0Hz) ,8.56 (1H,d,J=2.1Hz), 9.72 (1H,brs).
IR ν_{max} (KBr) : 3231,1744,1486,1317,1136 cm^{-1}.

Example 26

2-[4-(5-chloro-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methanesulfonylphenyl]oxazole-4-carboxylic acid

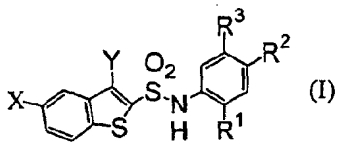
[0078] In the same manner as in Example 24, 68 mg of the title compound was obtained as colorless powder from 70 mg of methyl 2-[4-(5-chloro-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methanesulfonylphenyl]oxazole-4-carboxylate.
Melting point: 296-298°C
^{1}H-NMR (DMSO-d_6) : δ 2.58 (3H,s) ,3.37 (3H,s) ,7.55 (1H,dd,J=2.1 ,8.7Hz) ,7.62 (1H,d,J=8.7Hz) ,8.01 (1H,d, J=2.1Hz) ,8.09 (1H,d, J=8.4Hz) ,8.12 (1H,dd,J=2.1,8.4Hz) ,8.40 (1H,d,J=2.1Hz) ,8.83 (1H,s)
IR ν_{max} (KBr) : 3221,2924,1701,1485,1311,1153 cm^{-1}.

Example 27

Disodium 2-[4-(5-fluoro-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methanesulfonylphenyl]oxazole-4-carboxylate

[0079] Into 30 mL of methanol was dissolved 290 mg of methyl 2-[4-(5-fluoro-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methanesulfonylphenyl]oxazole-4-carboxylate, followed by addition of 77 mg of sodium methoxide. After 8 hours of stirring at room temperature, ether was added and the precipitated crystals were collected by filtration and washed with ether to obtain 300 mg of the title compound as colorless powder.
Melting point: 341-343°C
^{1}H-NMR (DMSO-d_6) : δ 2.49 (3H,s) ,3.42 (3H,s) ,7.26 (1H,ddd,J=2. 4,8.8,9.0Hz) ,7.40 (1H,dd,J=9.0,9.0Hz) ,7.56 (1H, dd,J=2.4,8.9Hz) ,7.89 (1H,dd,J=2.2,9.0Hz),7.95 (1H,d,J=9.0Hz) ,8.19 (1H,d,J=2 .2Hz).
IR ν_{max} (KBr) : 3490,1609,1570,1523,1470,1441,1400,1302,1280,1 119 cm^{-1}.
[0080] In the following, Compounds of Examples 28 to 49 were synthesized in the same manner as in Example 1.

Table 1



(I)

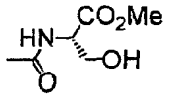
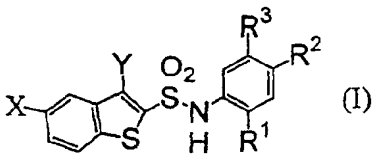
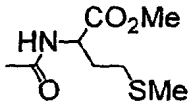
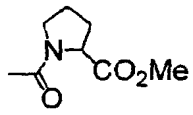
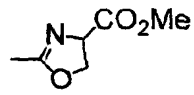
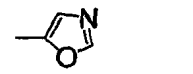
Example	X	Y	R^1	R^2	R^3
28	Cl	Me	H	NO_2	H
29	Cl	Me	H	CN	H
30	Cl	Me	H	COMe	H
31	Cl	Me	H	$CONH_2$	H
32	Cl	Me	H	$COCH_2SCH_2CO_2Me$	H
33	Cl	Me	OMe	NO_2	H
34	Cl	Me	NO_2	CN	H
35	Cl	Me	NO_2	NO_2	H
36	Cl	Me	NO_2	OMe	H
37	Cl	Me	OMe	$CONHCH_2CO_2Et$	H
38	Cl	Me	CO_2Me	OMe	OMe
39	Cl	Me	H	$SO_2(CH_2)_2CH_3$	H
40	H	Me	H	$SO_2(CH_2)_2CH_3$	H
41	Me	Me	H	$SO_2(CH_2)_2CH_3$	H
42	Cl	Me	SO_2Me	$CO_2CH(CH_3)_2$	H
43	Cl	Me	SO_2Me	$CONHCH_2CO_2Et$	H
44	Cl	Me	SO_2Me		H

Table 1 (cont'd)



(I)

Example	X	Y	R^1	R^2	R^3
45	Cl	Me	SO_2Me		H
46	Cl	Me	SO_2Me		H
47	Cl	Me	SO_2Me		H
48	F	Me	SO_2Me		H
49	F	Me	SO_2NEt_2	CO_2Me	H

Example 50

2-[4-(5-chloro-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methoxybenzoylamino]acetic acid

[0081] Into 25 mL of ethanol was dissolved 104 mg of the compound of Example 26, and 1 mL of 1 N aqueous sodium hydroxide solution was added at room temperature, followed by 15 hours of stirring at the same temperature. After confirmation of disappearance of the starting material, the solvent was removed by evaporation, followed by extraction with ether. After 2 mol/L hydrochloric acid was added to the aqueous layer, the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and then -dried over anhydrous sodium sulfate. The solvent was removed by evaporation and the resulting powder was washed with ether to obtain 97 mg of the title compound as light yellow powder.

Melting point: 282-285°C

^{1}H-NMR ($CDCl_3/CD_3OD$) : δ 2.50 (3H,s) ,3.82 (2H,s) ,3.84 (3H,s) ,7 .10-7.15 (2H,m) ,7.20-7.35 (2H,m) ,7.60-7.70 (2H, m).

IR ν_{max} (KBr) :3394,2974,1604,1554,1493,1412,1284,1230,1130 c m^{-1}.

Example 51

Sodium methyl 4-(5-chloro-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methanesulfonylbenzoate

[0082] Into 8 mL of THF was dissolved 115 mg of the compound of Example 1, followed by addition of 15 mg of sodium hydride (oily, 60%) at room temperature. After 1.5 hours of stirring at the same temperature, the solvent was removed by evaporation and the resulting powder was washed with ether to obtain 61 mg of the title compound as colorless powder.

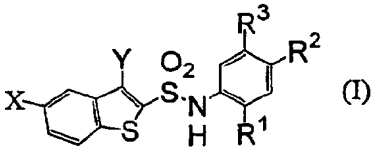
Melting point: >300°C

^{1}H-NMR (DMSO-d_6) : δ 2.51 (3H,s) ,3.37 (3H,s) ,3.72 (3H,s) ,7.39 (1H,d,J=2.1,8.8Hz) ,7.40 (1H,dd,J=1.8,8.5Hz) ,7.68 (1H,dd,J=1. 8,8.8Hz) ,7.80 (1H,d,J=1.8Hz) ,7.93 (1H,d,J=8.5Hz) ,8.23 (1H,d, J=1.8Hz) .

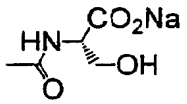
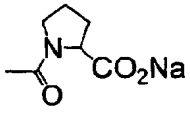
IR ν_{max} (KBr) :3448,1705,1597,1481,1442,1292,1134, 1103 cm^{-1}.

[0083] After the compounds of Examples 43, 44 and 46 were subjected to ester hydrolysis, the products were formed into sodium salts in the same conditions as in Example 51 to synthesize compounds of Examples 52, 53 and 54.

Table 2



(I)

Example	X	Y	R^1	R^2	R^3
52	Cl	Me	SO_2Me	$CONHCH_2CO_2Na$	H
53	Cl	Me	SO_2Me		H
54	Cl	Me	SO_2Me		H

[0084] The following show instrumental data in each Examples.

Table 3

Example	Melting point (°C)	H^1-NMR (δ)		IR (ν cm^{-1}, KBr)
28	Amorphous	$CDCl_3$	2.62(3H,s),7.29(2H,d,J = 9.1Hz),7.46(1H, dd,J=2. 0,8.7Hz),7.47(1H,brs), 7.73(1H,d, J=8.7Hz),7.7 6(1H,d,J=2.0Hz),8.15(2 H,d, J= 9.1Hz)	3248, 3084, 2925, 2856, 1596, 1521, 1342, 1160, 1113
29	226-227	$CDCl_3$/ CD_3OD	2.60(3H,s),7.29(2H,d,J = 9.0Hz),7.45(1H, dd,J=2. 1,8.7Hz),7.53(2H,d,J=9 .0Hz),7.75 (1H,d,J=2.1Hz), 7.76-7.77(1H,m)	3236, 2222, 1606, 1508, 1469, 1356, 1160
30	223-225	$CDCl_3$	2.53(3H,s),2.54(3H,s), 7.20-7.23(2H,m), 7.45(1H,dd, J=2.1,8.6Hz),7.72(2H,d , J=8.6Hz),7.88(2H,d,8. 6Hz)	3178, 2927, 2233, 1666, 1593, 1508, 1404, 1338, 1273, 1153
31	254-258	$CDCl_3$	2.55(3H,s),7.24(2H,d,J = 7.4Hz),7.36-7.45 (3H,m), 7.72(2H,d,J=8.6Hz)	3379, 3255, 3174, 2911, 2846, 2765, 1651, 1512, 1404, 1335, 1223, 1157
32	151-153	$CDCl_3$	2.57(3H,s),3.30(2H,s), 3.71(3H,s),3.93(2H, s), 7.20-7.25(2H,m),7.44-7.47(1H,m), 7.71-7.75(2H,m),7.86-7.90(2H,m)	3221, 3059, 2935, 1736, 1662, 1593, 1512, 1466, 1404, 1338, 1296, 1153

Table 3 (continued)

Example	Melting point (°C)	H^1-NMR (δ)		IR (ν cm^{-1}, KBr)
33	188-190	$CDCl_3$	2.63(3H,s),3.92(3H,s), 7.45(1H,dd, J=2.0,8.8Hz),7.63(1H,brs),7.67(1H ,d, J=2.4Hz),7.71(1H,d, J=8.8 Hz),7.76(1H,d, J=2.0Hz) 7.84(1H,dd,J=2.4,8.8Hz)	3293, 3088, 2930, 2846, 1735, 1596, 1525, 1500, 1442, 1402, 1342, 1281, 1254, 1163, 1130
34	204-206	$CDCl_3$	2.71(3H,s),7.51(1H,dd, J=2.0,8.6Hz),7.76 (1H,d ,J=8.6Hz),7.83(1H,dd,J =2.0, 8.8Hz), 7.85(1H,d,J=2.0 Hz),8.12(1H,d,J=8.8Hz) , 8.51(1H,d,J=2.0Hz)	3234, 3081, 2923, 2235, 1620, 1561, 1538, 1499, 1415, 1360, 1324, 1278, 1164, 1145, 1113
35	162-164	$CDCl_3$	2.71(3H,s),7.50(1H,dd, J=2.0,8.6Hz),7.74 (1H,d ,J= 8.6Hz),7.80(1H,d,J=2.0 Hz),8.15 (1H,d,J=9.4Hz) , 8.43(1H,dd,J=2.5,9.4Hz), 9.08(1H,d,J=2.5Hz)	3398, 3232, 1604, 1493, 1423, 1346, 1165
36	120-122	$CDCl_3$	2.52(3H,s),3.82(3H,s), 7.18-7.22(1H,m), 7.42-7.50(2H,m),7.67-7.73(2H,m),7.88(1H, d,J =9.2Hz)	3325, 3078, 2931, 2838, 1905, 1619, 1523, 1439, 1346, 1265, 1153
37	196-198	$CDCl_3$	1.30(3H,t,J-=7.2Hz),2.55(3H,s),3.7 7(3H, s),4.18(2H,d,J-=4.9Hz),4.25(2H,q,J-=7.2Hz),7.33(1H,d,J-=1.8Hz), 7.40-=1.8Hz), 7.40-7.45(2H,m),7.60-7.75 (3H,m)	3278, 1743, 1639, 1550, 1508, 1408, 1350, 1215, 1165

Table 3 (continued)

Example	Melting point (°C)	H^1-NMR (δ)		IR (ν cm^{-1}, KBr)
38	203-205	$CDCl_3$	2.56(3H,s),3.82(6H,s), 3.96(3H,s),7.30(1H, s), 7.41(1H,s),7.39-7.44(1H,m),7.67(1H,s), 7.68-7.75(1H,m)	3444, 3170, 2947, 1678, 1612, 1520, 1442, 1362, 1257, 1207, 1161
39	181-183	$CDCl_3$	0.96(3H,t,J=7.6Hz),1.6 9(2H,sext, J=7.6Hz),2.5 8(3H,s),3.00(2H,t,J=7. 6Hz), 7.31(2H,d,J=8.8H z),7.47(1H,dd,J=2.1,8. 7Hz),7.72(1H,d,J=8.7Hz),7.74(1H,d, J=2.1Hz),7 ' .79(2H,d,J=8.8Hz)	3217, 2966, 1 593, 1493, 14 04, 1350, 128 8, 1238, 1142 1088
40	201-203	$CDCl_3$	0.95(3H,t,J=7.9Hz),1.6 6(2H,sext, J=7.9Hz),2.6 7(3H,s),3.05(2H,t,J=7. 9Hz), 7.40(2H,d,J=9.0Hz),7.4 7(1H,td, J=7.9,1.5Hz),7 .51(1H,td,J=7.9,1.5Hz) , 7.74(2H,d,J=9.0Hz),7. 84(2H,dt, J=7.9,1.5Hz)	3195, 3058, 2930, 2878, 1594, 1497, 1489, 1346, 1281, 1160, 1132
41	201-203	$CDCl_3$	0.96(3H,t,J=7.7Hz),1.6 9(2H,sext, J=7.7Hz),2.4 9(3H,s),2.59(3H,s),3.0 0(2H,t, J=7.7Hz),7.11(1 H,s), 7.30(2H,d,J=8.6Hz), 7.3 4(1H,d,J=8.4Hz),7.56(1 H,s),7.68(1H,d, J=8.4Hz),7.78(2H,d,J=8.6Hz)	3194, 3059, 2962, 2877, 1593, 1493, 1400, 1342, 1292, 1138
42	164-166	$CDCl_3$	1.33(6H,d,J=6.2H),2.70 (3H,s),3.06(3H,s), 5.22 (1H,q,6.2Hz),7.47(1H,d d,J= 2.1,8.8Hz),7.74(1H, d,J=8.8Hz),7.79(lH,d,J =1.5Hz),7.85(1H,d,J=8. 6Hz), 8.18(1H,d, J=8.6Hz),8.4 8(1H,d,J=1.5Hz),9.82(1 H,s)	3410, 3244, 2924, 1709, 1604, 1500, 1350, 1304, 1153

Table 3 (continued)

Example	Melting point (°C)	H^1-NMR (δ)		IR (ν cm^{-1}, KBr)
43	88-90	CD_3OD	1.25(3H,t,J=7.2Hz),2.6 4(3H,s),3.19(3H, brs),4 .05(2H,s),4.17(2H,q,J= 7.2Hz)7.45 (1H,d,J=8.7H z),7.75(1H,brd,J=6.9Hz),7.85 (1H,d,J=8.7Hz),7 .87(1H,s), 7.96(1H,brd, J=6.9Hz), 8.34(1H,d,J=1.8Hz)	3359, 3232, 3078, 2989, 2927, 1739, 1655, 1604, 1485, 1304, 1211, 1161, 1134
44	154-156	CD_3OD	2.65(3H,s),3.07(3H,s), 3.73(3H,s),3.89(lH, dd,J =4.2Hz,11.4Hz),3.95(1H, dd, J=54,11.4Hz),4.68(1 H, dd,J=4.2,5.4Hz), 7.47(1H,dd,J=2.1,8.4Hz) ,7.85(2H,dd, J=2.1,8.7Hz),7.91(H,d,J=2.1Hz),8.0 9(1H, dd,J= 2.1,8.7 Hz),8.36(1H,d,J= 2.1Hz)	3220, 2924, 1736, 1643, 1608, 1496, 1303, 1161 1130
45	Amorphous	$CDCl_3$	2.10 (3H, s), 2.20 (2H, m), 2.56 (2H, m), 2.70 (3H, s), 3.05 (3H, s), 3.78 (3H, s), 4.89 (1H, m), 7.09 (1H, brs), 7.48 (1H, brm), 7.87 (2H, m), 7.96 (1H, m) , 8.29 (1H, brs), 9.73 (1H, brs)	3230, 2921, 2853, 1739, 1653, 1604, 1541, 1492, 1440, 1393, 1353, 1307, 1226, 1166, 1131, 1105
46	Amorphous	$CDCl_3$	2.00-2.30(4H, m), 2.70 (3H, s), 2.98 (3H, 5), 3.50-3.65 (2H, m), 3.76 (3H, s), 4.61 (1H, m), 7.48(1H, d, J=8.4 Hz), 7.75(1H,d, J=8.4Hz), 7.70-7.80 (3H, m) , 8.10 (1H, s) , 9.69 (1H, brs)	3228, 2952, 2925, 1741, 1631, 1496, 1423, 1390, 1353, 1308, 1281, 1203, 1167, 1133, 1107, 1080

Table 3 (continued)

Example	Melting point (°C)	H^1-NMR (δ)		IR (ν cm^{-1}, KBr)
47	Amorphous	$CDCl_3$	2.69 (3H, s), 3.01 (3H, s) , 3.80 (3H, s), 4.58 (1H, dd, J=9.0, 10.5 Hz) ,4.68 (1H, dd, J=8.1,9.0 Hz), 4.93 (1H, dd, J=8.1,10.5 Hz), 7.47 (1H, dd, J=2.1, 8.4 Hz), 7.73 (1H, d, J=8.4 Hz), 7.78 (1H, d, J=2.1 Hz), 7.86 (1H, d, J= 8.7 Hz), 8.14 (1H, dd, J=2.1, 8.7Hz), 8.43 (1H, d, J=2.1 Hz)	3224, 2958, 1739, 1500, 1308, 1161
48	199-201	DMSO-d_6	2.51(3H, s), 3.17(3H, s), 7.46(1H, ddd, J=1.8, 9.0, 9.0Hz), 7.52 (1H, d, J=8.4 Hz), 7.75 (1H, d, J= 1.8 Hz), 7.81 (1H, dd, J=1.8, 8.7 Hz), 7.98 (1H, dd, J= 1.8, 8.4Hz), 8.10 (1H, dd, J=4.8, 9.0Hz), 8.15 (1H, s) , 8.48 (1H, s)	3243, 3119, 1606, 1501, 1303, 1151
49	137-140	$CDCl_3$	1.14 (6H, t, J=7.1 Hz), 2.68 (3H, s), 3.31 (4H, q, J=7.1 Hz), 3.88 (3H, s), 7.29 (1H, ddd, J=2.1, 8.8, 8.8Hz), 7.45 (1H, dd, J=2.1, 8.8 Hz), 7.75 (1H, dd, J=4.8, 8.8 Hz), 7.84 (1H, d, J=8.6 Hz), 8.07 (1H, dd, J=2.0, 8.6 Hz), 8.35 (1H, d, J=2.0 Hz), 9.88 (1H, s)	3157, 3076, 2979, 2949, 1727, 1604, 1577, 1560, 1521, 1498, 1473, 1458, 1438, 1389, 1344, 1325, 1307, 1280, 1200, 1159, 1134, 1100
52	290-292	D_2O	2.50(3H,s),3.47(3H,s), 3.82(2H,s),7.22(1H, d,J= 8.7Hz),7.42(1H,dd,J=1.8 ,8.7Hz),7.69 (1H,dd,J=2. 1,8.7Hz),7.80(1H,d,J=8. 7Hz), 7.83(1H,d,J=2.1Hz) , 8.21(1H,d,J=1.8Hz)	3410, 1600, 1473, 1400, 1296, 1134, 1107

Table 3 (continued)

Example	Melting point (°C)	H^1-NMR (δ)		IR (ν cm^{-1}, KBr)
53	260	D_2O	2.47(3H,s),3.48(3H,s), 3.81(1H,dd, J=5.7Hz,11.4 Hz),3.87(1H,dd,J=3.6, 11.4Hz),4.38(1H,dd,J=3. 6,5.7Hz),7.24(1H, d,8.7H z),7.33(1H,d,J=8.7Hz),7 .68-7.73 (3H,m),8.24(1H,d,J= 2.1Hz)	3464, 1597, 1473, 1408, 1292, 1134, 1107
54	298	D_2O	1.66-1.78 (2H, m), 2.06-2.12 (2H, m), 2.32 (3H, s), 3.43 (3H, s), 3.37-3.48 (2H, m), 4.14 (1H, m), 6.99 (1H, d, J=8.7 Hz) , 7.10-7.25 (2H, m), 7.34-7.40 (2H, m), 7.51 (1H, d, J=8.7 Hz) , 7.95 (1H, d, J=1.8 Hz)	3419, 1599, 1436, 1308, 1105

[0085] Next, as for the representative compounds of the present invention, inhibitory activity of chymase and stability in rat plasma were investigated according to the following Test Examples.

Test Example 1

Measurement of inhibitory activity of simian chymase

[0086] It is known that chmase has a difference in substrate selectivity, depending on the species thereof. It was reported that a primary structure and enzymatic property of Simian chymase are significantly similar to those of human chymase (Miyazaki et al., Kekkan, Vol. 20, p. 207 (1997)).

[0087] Then, simian chymase used was obtained from the heart of rhesus monkey through purification in accordance with a Urata's human heart chymase purification method (which was reported in a document).

[0088] The inhibitory activity of the compounds of the present invention for chymase in vitro was obtained by the following methods.

[0089] Chymase activity was determined with reference to the method known in a literature (Miyazaki et al., Kekkan, Vol. 20, p. 207 (1997)). That is, the activity was measured by reacting free His-Leu formed together with Ang II with o-phthalaldehyde (hereinafter, abbreviated as OPT) to prepare a fluorescent derivative and determining the amount quantitatively by means of a fluorophotometer.

[0090] First, 3.6 μmol of each test compound was weighed in a test tube and was dissolved into 3 mL of DMSO. The DMSO solution was diluted 1000-fold with 20 mM Tris-hydrochloric acid buffer solution (pH 8.0) containing 0.01% Triton X-100 and 0.5 M potassium chloride to prepare 3.6×10^{-6} M solution, which was successively diluted with the buffer solution to prepare test sample solutions having concentrations of 3.6×10^{-6} M to 3.6×10^{-9} M. To 500 μL of the test sample solution of each concentration or buffer solution was added 50 μL of an enzyme solution, followed by 10 minutes of pre-incubation at 37°C. Then, 50 μL of 0.1 mM Ang I solution was added to initiate a reaction. Human angiotensin I (manufactured by SIGMA) was employed as Ang I. The enzyme (chymase) solution to be used for the reaction was adjusted so as to hydrolyze about 60% of substrate under the conditions, and the reaction wherein a buffer solution containing no enzyme was carried out as a blind test. After 120 minutes of incubation at 37°C, the reaction was terminated by adding 900 μL of trichloroacetic acid. Thereafter, the reaction mixture was centrifuged at 4°C at 3,000 rpm for 10 minutes and 2 mL of 2 N sodium hydroxide and 1 mL of methanol were added to 1 mL of the resulting supernatant. Thereto was added 100 μL of methanol solution containing 1.2 mg of N-acetyl-L-cysteine and 1 mg of OPT per 1 mL, whereby a derivatization reaction was initiated. After the reaction mixture was left on standing for exactly 1 hour, fluorescence intensity at fluorescence wavelength of 502 nm under excitation wavelength of 304 nm was measured. The measurement was repeated twice for each sample and blind test. The fluorescence intensity obtained by subtracting the average value at blind test from the average value thereof was determined as chymase activity.

[0091] In this regard, an enzymatic reaction using a buffer solution instead of the test sample solution was carried out as a control, and inhibitory ratio of chymase activity was determined as percentage by dividing the difference of subtraction of the activity at the addition of the test compound from the chymase activity at the control by the chymase activity at the control. Based on each inhibitory ratio, the concentration at which 50% of the activity was inhibited (hereinafter, referred to as IC_{50} value) was calculated.

Test Example 2

Measurement of cathepsin G inhibitory activity and chymotrypsin inhibitory activity

[0092] Each activity of cathepsin G or chymotrypsin was measured by determining the amount of free p-nitroanilide quantitatively using a synthetic substrate which is colorless and yields colored products upon hydrolysis by means of a spectrophotometer. Chymotrypsin Type I-S derived from bovine pancreas was purchased from SIGMA. As cathepsin G, the product of Elastin Products Company, Inc. derived from human purulent sputum was used. Suc-Ala-Ala-Pro-Phe-pNA (manufactured by SIGMA) was used as the synthetic substrate. An inhibitory effect of a compound on each enzyme was determined by the following method.

[0093] Each test compound (5 μmol) was weighed in a test tube and dissolved into 2 mL of DMSO. The DMSO solution was diluted 100-fold with 20 mM Tris-hydrochloric acid buffer solution (pH 7.5) containing 0.01% Triton X-100 and 0.5 M potassium chloride to prepare 3.6×10^{-6} M solution, which was successively diluted to prepare test sample solutions having concentrations of 3.6×10^{-6} M to 3.6×10^{-9} M. To 200 μL of each test sample solution or buffer solution was added 100 μL of an enzyme solution of 40 μg/mL chymotrypsin or 8 units/mL cathepsin G, followed by 10 minutes of pre-incubation at 37°C. Then, 200 μL of 1 mM substrate solution was added to initiate an enzymatic reaction under a temperature of 37°C. A reaction wherein a buffer solution containing no enzyme was carried out as a blind test, and incubation time was 30 minutes and 60 minutes for chymotrypsin and cathepsin G, respectively. After the incubation, the reaction was terminated by adding 300 μL of 50% acetic acid, and absorbance at 405 nm was measured. The measurement was repeated twice for each sample and blind test. The absorbance obtained by subtracting the average value at blind test from the average value of each sample was determined as activity of each enzyme.

[0094] In this regard, an enzymatic reaction using a buffer solution instead of the test sample solution was carried out as a control, and inhibitory ratio of each enzyme activity was determined as percentage by dividing the difference from the subtraction of the activity at the addition of the test compound from the enzyme activity at the control by the enzyme activity at the control. Based on each inhibitory ratio, IC_{50} value was calculated.

[0095] Table 3 shows IC_{50} values of simian chymase inhibitory activity of the representative compounds as well as cathepsin G inhibitory activity and chymotrypsin inhibitory activity thereof.

Table 4

Inhibitory specificity of active compounds			
Compound	IC_{50} value (nmol/L)		
	Chymase	Chymotrypsin	Cathepsin G
Chymostatin	287	9.67	5.99
Example 1	50	>10000	>10000
Example 2	42		
Example 3	178		
Example 4	111	>10000	>10000
Example 5	150	>1000	>1000
Example 7	185	>1000	>1000
Example 8	159	>10000	>10000
Example 11	100		
Example 13	271		
Example 14	278	>10000	>10000
Example 17	9	>10000	>10000

Table 4 (continued)

Inhibitory specificity of active compounds			
Compound	IC_{50} value (nmol/L)		
	Chymase	Chymotrypsin	Cathepsin G
Example 19	20		
Example 20	39		
Example 24	2	>10000	>10000
Example 25	75		
Example 26	10	>10000	>10000
Example 52	157		

Test Example 3

Stability in rat plasma

[0096] Stability of the compounds of the invention in rat plasma was investigated.

[0097] Male SD rats (7-week-old) were anesthetized with ether under over-night fasting conditions and, after an abdominal part was incised, blood was collected from aorta abdominalis using a heparinized disposable plastic syringe. The blood was centrifuged under cooling to collect a supernatant plasma. The collected plasma was stored under freezing at -30°C and was melted before use. After a test compound was dissolved in DMSO, the solution was added to 200 μL of the plasma so as to be 10 μg/mL, followed by incubation at 37°C. After 60 minutes, the mixture was acidified by adding 200mL of 0.1 mol/L hydrochloric acid, and then extracted twice with 2 mL of ethyl acetate. The resulting organic layer was evaporated to dryness under a nitrogen gas flow and the residue was dissolved into 200 μL of acetonitrile to prepare a sample solution. On the other hand, the test compound was dissolved into 1% DMSO-acetonitrile so as to be 10 μg/mL as a control solution. The sample solution and control solution was investigated by high performance liquid chromatography (hereinafter, abbreviated as HPLC). Residual ratio (%) was determined as percentage by dividing the peak area of the sample solution by that of the control solution.

HPLC conditions:

[0098]

Column: Waters Nova Pack C_{18} (inner diameter: 3.9 mm, length: 150 mm)
Mobile phase A: acetonitrile/water = 10/90
Mobile phase B: acetonitrile/methanol = 50/50
Eluent: Mobile phase A-mobile phase B (100/0 to 0/100, linear gradient, 50 minutes)
Flow rate: 1.0 mL/minute
Amount of injection: 50 μL

[0099] Table 4 shows residual ratios of representative compounds in rat plasma.

Table 5

Compound	Residual ratio in rat plasma (%)
Example 1	93.9
Example 4	93.5
Example 5	85.2
Example 7	96.4
Example 8	92.0
Example 14	79.2
Example 19	96.2

Table 5 (continued)

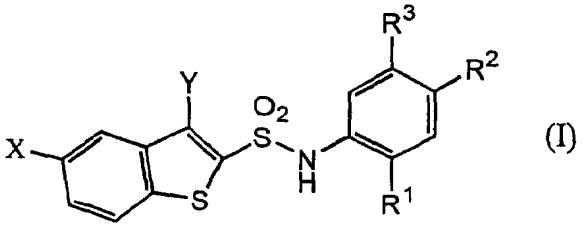
Compound	Residual ratio in rat plasma (%)
Example 24	100
Example 26	100

INDUSTRIAL APPLICABILITY

[0100] The N-substituted benzothiophenesulfonamide derivatives or pharmaceutically acceptable salts thereof of the invention have a selective inhibitory action on chymase and are useful as agents for preventing or treating cardiac and circulatory diseases, especially cardiac infarction, restenosis after PTCA and intimal thickening after bypass grafting caused by abnormal increase of production of angiotensin II or endothelin I based on chymase activity.

Claims

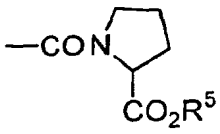
1. An N-substituted benzothiophenesulfonamide derivative represented by formula (I):



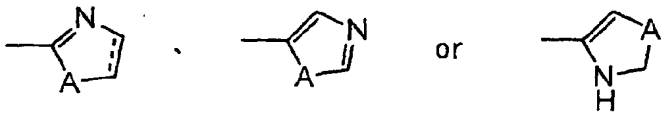
(I)

wherein

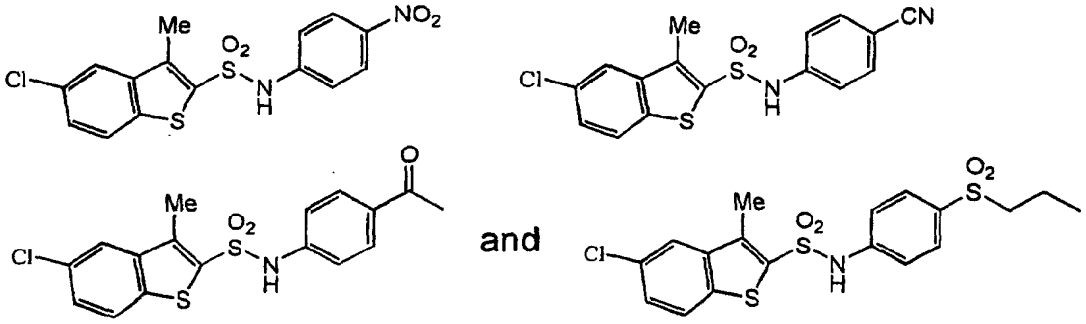
X represents a hydrogen atom, a halogen atom or a lower alkyl group;
Y represents a lower alkyl group;
R^1 and R^2 each may be the same or different and represents a hydrogen atom, a lower alkoxycarbonyl group, a lower alkylsulfonyl group, a benzoyl group, an acyl group having 1 to 4 carbon atoms, a lower alkoxy group, a lower alkoxycarbonylmethylthioacetyl group, a nitro group, $-CONHR^4$ in which R^4 represents a hydrogen atom, a lower alkoxycarbonylmethyl group, a carboxymethyl group or $-CH(CH_2OH)COOR^5$ in which R^5 represents a hydrogen atom or a lower alkyl group, a group represented by formula:



in which R^5 has the same meaning as above, a monocyclic heterocyclic group represented by formulae which may be substituted by $-CO_2R^5$ in which R^5 has the same meaning as above:



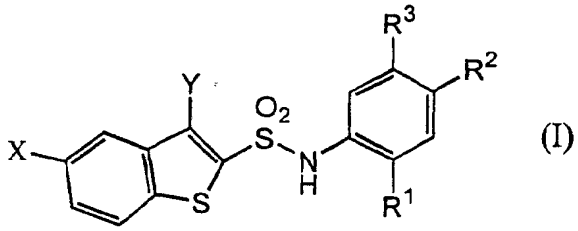
in which A represents an oxygen atom, a sulfur atom or NH and the dotted part represents a single bond or a double bond, a hydroxy lower alkyl group, a cyano group provided that R^1 and R^2 are not hydrogen atoms at the same time; and R^3 represents a hydrogen atom, a lower alkoxy group or a lower alkyl group, except the compounds represented by formulae:



or a salt thereof.

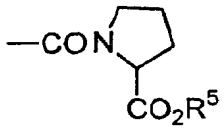
2. The N-substituted benzothiophenesulfonamide derivative according to claim 1, wherein said derivative or a salt thereof is selected from the group consisting of methyl 4-(5-chloro-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methanesulfonylbenzoate, sodium methyl 4- (5-chloro-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methanesulfonylbenzoate, isopropyl 4-(5-chloro-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methanesulfonylbenzoate, 5-chloro-3-methylbenzo [b] thiophene-2-sulfonic acid (4-acetyl-2-methanesulfonylphenyl)amide, 5-chloro-3-methylbenzo[b]thiophene-2-sulfonic acid (4-benzoyl-2-methanesulfonylphenyl)amide, methyl 4-(5-fluoro-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methanesulfonylbenzoate, methyl 4-(5-methyl-3-methylbenzo[b] thiophene-2-sulfonylamino)-3-methanesulfonylbenzoate, 5-fluoro-3-methylbenzo[b]thiophene-2-sulfonic acid (4-acetyl-2-methanesulfonylphenyl)amide, methyl 4-(3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methanesulfonylbenzoate, 2-[4-(5-chloro-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methanesulfonylphenyl]oxazole-4-carboxylic acid, 2-[4-(5-fluoro-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methanesulfonylphenyl]oxazole-4-carboxylic acid, disodium 2-[4-(5-chloro-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methanesulfonylphenyl]oxazole-4-carboxylate, and disodium 2-[4-(5-fluoro-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methanesulfonylphenyl]oxazole-4-carboxylate.

3. A chymase inhibitor comprising the N-substituted benzothiophenesulfonamide derivative represented by formula (I):

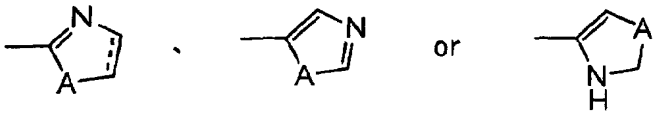


(I)

wherein X represents a hydrogen atom, a halogen atom or a lower alkyl group;
Y represents a lower alkyl group;
R^1 and R^2 each may be the same or different and represents a hydrogen atom, a lower alkoxycarbonyl group, a lower alkylsulfonyl group, a benzoyl group, an acyl group having 1 to 4 carbon atoms, a lower alkoxy group, a lower alkoxycarbonylmethylthioacetyl group, a nitro group, -CONHR^4 in which R^4 represents a hydrogen atom, a lower alkoxycarbonylmethyl group, a carboxymethyl group or -CH(CH_2OH)COOR^5 in which R^5 represents a hydrogen atom or a lower alkyl group, a group represented by formula:



in which R^5 has the same meaning as above, a monocyclic heterocyclic group represented by formulae which may be substituted by $-CO_2R^5$ in which R^5 has the same meaning as above:



in which A represents an oxygen atom, a sulfur atom or NH and the dotted part represents a single bond or a double bond, a hydroxy lower alkyl group, a cyano group provided that R^1 and R^2 are not hydrogen atoms at the same time; and R^3 represents a hydrogen atom, a lower alkoxy group or a lower alkyl group, or a salt thereof.

4. A pharmaceutical composition comprising the N-substituted benzothiophenesulfonamide derivative or a salt thereof as defined in claim 3.

5. An agent for preventing or treating cardiac infarction, restenosis after percutaneous transluminal coronary angioplasty, and intimal thickening after bypass grafting, wherein the agent comprises the N-substituted benzothiophenesulfonamide derivative or a salt thereof as defined in claim 3.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP01/08061

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl[7] C07D333/62, 409/12, 413/12, 417/12, A61K31/381, 4025, 4178, 422, 427, A61P43/00, 9/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int.Cl[7] C07D333/62, 409/12, 413/12, 417/12, A61K31/381, 4025, 4178, 422, 427, A61P43/00, 9/10

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAPLUS, REGISTRY (STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00/12623 A2 (SmithKline Beecham P.L.C.), 09 March, 2000 (09.03.00), & AU 9959706 A	1-5
A	WO 99/42465 A2 (SmithKline Beecham P.L.C.), 26 August, 1999 (26.08.99), & EP 1066288 A2	1-5
A	WO 96/31492 A1 (Texas Biotechnology Corporation), 10 October, 1996 (10.10.96), & US 5594021 A & AU 9655367 A & EP 819125 A1 & BR 9604875 A & JP 11-507015 A & US 5962490 A & NO 9704577 A & US 2001021714 A & AU 9935803 A & US 5594021 A & US 5464853 A & US 5514691 A & US 5591761 A & US 5571821 A & CA 2217169 A & CN 1184470 A & EP 1048657 A1 & US 5962490 A	1-5

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 November, 2001 (13.11.01)	27 November, 2001 (27.11.01)
Name and mailing address of the ISA/ Japanese Patent Office	Authorized officer
Facsimile No.	Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP01/08061

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JP 2000-95770 A (Toa Eiyo, Ltd.), 04 April, 2000 (04.04.00) (Family: none)	1-5
PA	JP 2001-97946 A (Mitsubishi Chemical Corporation), 10 April, 2001 (10.04.01) (Family: none)	1-5
A	WO 97/11941 A1 (Suntory, Limited), 03 April, 1997 (03.04.97), & EP 795548 A1 & US 5814631 A	1-5

Form PCT/ISA/210 (continuation of second sheet) (July 1992)